United States
Environmental Protection
Agency

EPA/690/R-06/021F
Final
8-03-2006

Provisional Peer Reviewed Toxicity Values for

4,4'-Methylenebis (2-chloroaniline)
(CASRN 101-14-4)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

8-3-2006

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 4,4'-METHYLENEBIS (2-CHLOROANILINE) (CASRN 101-14-4)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The HEAST (U.S. EPA, 1997) includes subchronic and chronic oral RfDs of 7E-4 mg/kg-day for 4,4'-methylenebis(2-chloroaniline) (MOCA) that were based on liver and urinary bladder effects in dogs given an average daily dose of 7.3 mg/kg-day of MOCA via gelatin capsules for 9 years by Stula et al. (1977). An uncertainty factor of 10,000 was applied to the LOAEL. The source of this assessment was a Health and Environmental Effects Document (HEED) (U.S. EPA, 1990). No RfD assessment for MOCA is available on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). Other than the HEED discussed above, the CARA list (U.S. EPA, 1991, 1994) does not include any relevant documents. ATSDR (1994) derived a chronic oral MRL of 0.003 mg/kg-day for MOCA, based on a LOAEL of 10 mg/kg-day for hepatic effects (liver hyperplasia, increased serum ALT) in the Stula et al. (1977) dog study and an uncertainty factor of 3000. ATSDR

(1994) did not derive an acute or an intermediate duration oral MRL due to lack of data. WHO (2002) has not assessed the toxicity of MOCA.

The HEAST (U.S. EPA, 1997) does not provide an RfC for MOCA, reporting that a chronic inhalation RfC was considered not verifiable by the RfD/RfD Work Group (2/10/93). U.S. EPA (1990) concluded that inhalation data were inadequate for quantitative risk assessment. An RfC for MOCA is not available on IRIS (U.S. EPA, 2005a). ATSDR (1994) did not derive MRLs for inhalation exposure due to the lack of suitable data. ACGIH (2001, 2002) has established a TLV-TWA of 0.01 ppm (0.11 mg/m^3) for MOCA in order to protect against cyanosis, methemoglobinemia, adverse effects on the kidney, and cancer in the bladder and other tissues in workers. The NIOSH (2002) REL-TWA is 0.003 mg/m^3. OSHA (2002) has not established a PEL for this chemical.

MOCA is listed on the HEAST (U.S. EPA, 1997) as a Group B2 carcinogen with an oral slope factor of 1.3E-1 $(mg/kg\text{-}day)^{-1}$ based on lung tumors in 2-year rat studies by Stula et al. (1975) and Kommineni et al. (1978). The HEAST also reports an inhalation unit risk of 3.7E-5 $(\mu g/m^3)^{-1}$ based on route-to-route extrapolation from the oral data. The HEED (U.S. EPA, 1990) was the source document for this assessment. A cancer assessment for MOCA is not available on IRIS (U.S. EPA, 2005a) or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). IARC (1993) classified MOCA into Group 2A, *probably carcinogenic to humans,* and ACGIH (2002) put MOCA in Group A2 as a suspected human carcinogen. NTP (2002) has not performed a cancer bioassay for MOCA.

Literature searches were conducted from 1989 to 2002 for studies relevant to the derivation of provisional toxicity values for MOCA. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK and DART/ETICBACK. Additional literature searches were conducted by NCEA-Cincinnati from 2002 through April 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

Epidemiological studies of MOCA in human workers are limited. The studies have primarily been designed to look for bladder cancer, as MOCA is structurally similar to benzidine, which is known to produce bladder tumors in humans, and MOCA has been shown to produce bladder tumors in animal studies.

Linch et al. (1971) compared a group of 31 active MOCA-exposed workers at a chemical production facility (average age of 50 years; MOCA exposure ranging from 6 months to 50 years) to 31 control workers at the plant without MOCA exposure with regard to overall health classification, frequency and duration of absenteeism, type of illness, and urinary sediment examination. There were no differences between active MOCA workers and controls. No malignancies or deaths occurred in either group. The researchers further compared another group of 178 employees who had worked with MOCA at one time, but not for at least 10 years, with the plant population as a whole using the same endpoints. Again, no differences were found. Two deaths due to malignancy were recorded among the 178 early exposure MOCA workers, but in both cases, the original diagnosis (laryngeal carcinoma, carcinoma of the large bowel) and surgery occurred prior to the earliest MOCA exposure. Continued monitoring by annual urinary analysis and cytology revealed no cases of bladder cancer through November, 1981 among the early exposure MOCA workers still employed by the company (workers who left the company were not monitored for cancer incidence) (Ward et al., 1987).

Ward et al. (1988) studied the incidence of bladder cancer among workers exposed to MOCA between 1968-1979 at a Michigan chemical plant. Exposure concentrations were not quantified. Urine samples were submitted by 370 of the 540 eligible workers. No positive cytology results were found. However, examination of a 28-year old worker with low-grade intermittent hematuria found a bladder tumor. Cystoscopy was then offered to 77 workers with atypical cells or slight hematuria in the initial screening and 83 workers whose job histories suggested the highest exposures to MOCA. Of these, 67 agreed to have the examination, and a bladder tumor in a second young male worker was found. Both tumors were found in men under 30 years of age who had never smoked. Tumors in both workers were small, non-invasive papillary neoplasms that would not have been detected without systematic screening. The prevalence of low grade tumors in asymptomatic males of this age group is not known, but the incidence of clinically apparent tumors in men aged 25-29 is only 1 per 100,000. Although this finding is based on only 2 cases, the researchers considered it to be consistent with the hypothesis that MOCA induces bladder cancer in humans. A third case of a worker with papillary transitional cell carcinoma was subsequently detected; however, that worker was excluded from the analysis because the worker was a smoker, was exposed to MOCA for only 1.5 months, and subsequently worked at other positions in the chemical industry that may have resulted in exposure to other chemicals (Ward et al., 1990). This study provides only limited evidence for an association between exposure to MOCA and bladder cancer in humans (based on only two cases, no internal control group, exposure to other chemicals not excluded), and is not useful for quantitative risk assessment because exposure was not quantified.

Animal Studies

Animal studies of MOCA have been designed primarily as cancer bioassays. Studies are available for rats, mice, and dogs.

In an early study from the German literature (Grundmann and Steinhoff, 1970; Steinhoff and Grundmann, 1971), groups of 25 Wistar rats of each sex were given a low protein diet containing 0 or 0.1% (1000 ppm) of MOCA for 500 days. The cumulative dose in the treated groups was estimated by the researchers at 27 g/kg, corresponding to an average daily dose of 54 mg/kg-day. After 500 days, all rats received untreated diet for the remainder of their lives. The average survival time was reduced in treated rats (565 and 535 days in males and females, respectively) compared with controls (730 days). Among treated rats, 23 males and 20 females died with tumors. Liver tumors (hepatomas) were observed in 22/25 treated males and 18/25 treated females compared with 0/25 in controls of both sexes ($p<0.001$ by Fisher exact test). Lung tumors (mainly carcinomas) were observed in 8/25 treated males ($p=0.002$ by Fisher exact test) and 5/25 treated females ($p=0.025$ by Fisher exact test) compared with 0/25 in controls of both sexes. Statistical analysis of these results was performed by IARC (1993). Two mammary adenomas were also observed in treated females.

Stula et al. (1975), exposed groups of 50 male and 50 female Charles River CD rats to 0 or 1000 ppm (50 mg/kg-day, assuming a rat consumes a daily amount of food equal to 5% of its body weight) of MOCA (95% pure) added to a standard diet (23% protein) for up to 2 years. Six rats from each group were sacrificed after one year for interim evaluation. Terminal sacrifice for a group was performed when only six animals remained alive in that group. All rats placed on the study were necropsied, and 30 tissues from each rat were microscopically examined. Tumor incidence was evaluated using the chi-square test ($p<0.05$). Survival appeared to be reduced in treated rats; 50% survival was reached after 581 days in treated males and females, compared with 626 and 677 days in control males and females, respectively. Body weight and food consumption were not reported (and may not have been measured). The results of the interim sacrifice were not reported separately, although it was mentioned that adenomatosis, a preneoplastic or early neoplastic lesion in the lung that progressed to adenocarcinoma, was seen as early as one year on test. At terminal sacrifice, examination of the lung showed statistically significant increased incidences of adenomatosis in males (14/44 vs 1/44 in controls) and females (11/44 vs 1/44 in controls) and adenocarcinoma in males (21/44 vs 0/44) and females (27/44 vs 0/44). Related findings that were not statistically significant, but are noteworthy because of their rarity, were squamous cell carcinomas in 1 treated male and 1 treated female, and pleural cavity biphasic tumors (similar to mesotheliomas) in 4 treated males and 2 treated females. Neither of these tumors were seen in controls. Focal pleural and/or pericardial hyperplasia was typically seen adjacent to lung adenocarcinomas. The only other noteworthy findings occurred in the liver. Liver tumors were found in treated male (3/44 hepatocellular adenoma, 3/44 hepatocellular carcinoma) and female (2/44 hepatocellular adenoma, 3/44 hepatocellular carcinoma) rats, but

not in controls of either sex. The differences from controls were not statistically significant, however. The neoplastic lesions in the liver were accompanied by hepatocytomegaly, fatty change, necrosis, bile duct proliferation, and fibrosis, although no details were provided regarding the incidence or severity of the nonneoplastic lesions.

As part of the same study, Stula et al (1975) exposed 25 additional rats per sex to 0 or 1000 ppm (50 mg/kg-day, as above) of MOCA (95% pure) in a protein restricted diet (7% protein). Four animals of each sex from the control and treated groups were sacrificed after one year of treatment; those animals were not included in the analysis of tumor incidence. The low protein diet caused a reduction in survival compared with the standard diet, so that the test was ended after 16 months. Survival appeared to be slightly lower in the MOCA treated group (50% survival at 432 and 438 days in males and females, respectively) than in controls (50% survival at 476 and 483 days in males and females, respectively). The development of lung tumors was similar to the standard diet study, with statistically significant increases in adenomatosis in males (8/21 vs 1/21 in controls) and females (14/21 vs 1/21 in controls) and adenocarcinoma in males (5/21 vs 0/21 in controls) and females (6/21 vs 0/21 in controls), and a pleural cavity biphasic tumor in 1 treated male (and no controls). In the liver, the nonneoplastic lesions were similar to those seen in the standard diet study. However, the incidences of hepatocellular adenomas (5/21) and carcinomas (11/21) in male rats were statistically significantly increased (0/21 in controls). Lower incidences of these tumors were found in treated females (2/21 adenoma, 1/21 carcinoma). In females, there was a statistically significant increase in the incidence of mammary adenocarcinoma (6/21 vs 0/21 in controls), corresponding to a significant decrease in mammary fibroadenoma (1/21 vs 7/21 in controls).

Kommineni et al. (1978) exposed male Sprague-Dawley rats (50 - 100 per dose) to industrial grade MOCA (unspecified purity) in protein sufficient diets (27% protein) at 0, 250, 500, or 1000 ppm, or in protein restricted diets (8% protein) at 0, 125, 250, or 500 ppm for 18 months, followed by a 6-month recovery period. Based on the assumption that a rat consumes a daily amount of food equal to 5% of its body weight, low-, mid-, and high-dose rats received approximately 12.5, 25, and 50 mg/kg-day in the protein sufficient dose group and 6.25, 12.5, and 25 mg/kg-day in the protein restricted groups. The following parameters were evaluated: survival, food consumption, body weight, size and location of palpable masses, selected hematology parameters (hematocrit and hemoglobin; 10 rats per dose on 5 occasions over 72 weeks), and urinalysis (volume, specific gravity, and urine MOCA concentration were determined on 4 occasions over 52 weeks). All rats that died before the conclusion of the study were autopsied, and all survivors at the end of the study were sacrificed and autopsied. Gross lesions and major organs (lungs, liver, kidney, spleen, pancreas, adrenals, pituitary, thyroid, urinary bladder, brain, and gross lesions) were examined microscopically.

Survival was reduced in all treated groups in a dose-related manner (Kommineni et al., 1978). Mean survival times for the control, low-, mid-, and high-dose groups were 89, 87, 80,

and 65 weeks, respectively, in the protein-adequate study (statistically significantly reduced in the mid- and high-dose groups) and 87, 81, 79, and 77 weeks, respectively, in the protein-deficient study (statistically significantly reduced in the high-dose group). In general, body weights of protein-deficient rats were lower than those of protein-adequate rats. In both studies, body weights of high-dose rats were reduced compared to their respective controls, starting at approximately 20 weeks and continuing throughout the study. Body weights of rats in the other groups were generally similar to controls. Food consumption in all treated groups at all time periods was generally within 11% of control values. Hematocrit and hemoglobin values showed slight decreases relative to controls in the high-dose groups in both the protein-adequate and protein-deficient studies, but were within historical control ranges. Noncancer lesions observed during the microscopic examinations were not reported. Increased incidences of pulmonary adenomas and adenocarcinomas, mammary adenocarcinomas, Zymbal gland carcinomas, and hepatocellular carcinomas were observed in animals exposed to MOCA in either of the diets compared with controls (Table 1). Increased incidences of these tumors were attributed to MOCA exposure. Metastasis of these neoplasms to other organs, such as kidneys, pituitary gland, and pancreas, was also noted.

Russfield et al. (1975) exposed male Charles River CD-1 (Sprague-Dawley-derived) rats (25 per dose) and male and female Charles River CD-1 (HaM/ICR-derived) mice (25 per sex and dose) to MOCA (hydrochloride salt), 98% pure in the diet at 0, 500 or 1000 ppm (rats), or 0, 1000 or 2000 ppm (mice) for 18 months. Dietary concentrations (ppm) were converted to mg/kg-day by assuming that a rat consumes a daily amount of food equal to 5% of its body weight and a mouse consumes a daily amount of food equal to 15% of its body weight. Therefore, low- and high-dose rats were estimated to receive 25 and 50 mg/kg-day, respectively, of the hydrochloride salt (21.5 and 43.0 mg/kg-day, respectively, of MOCA), and low- and high-dose mice were estimated to receive 150 and 300 mg/kg-day, respectively, of the hydrochloride salt (129.5 and 259 mg/kg-day, respectively, of MOCA). Surviving animals were maintained on untreated diet for an additional 6 months after treatment. The following parameters were evaluated: clinical signs of toxicity (daily), body weight (unspecified intervals), food consumption (first 20-25 weeks), gross pathology (animals that survived $\geq$6 months or killed *in extremis*), and microscopic pathology of the lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, unspecified reproductive organs, gross lesions, and (in rats) pituitary. Tumor incidence was statistically evaluated using the Fisher exact test.

Table 1. Tumor Incidence in Male Rats Exposed to MOCA in the Diet for 18 Months Followed by a 6-Month Recovery Period (Kommineni et al., 1978)

Tumor	Protein-Adequate Diet		Protein-Restricted Diet	
	Dose Group (ppm)	Incidence (%)	Dose Group (ppm)	Incidence
Lung, adenocarcinoma	0 250 500 1000	0/100 (0) 14/100 (14) *** 20/75 (27) *** 31/50 (62) ***	0 125 250 500	0/100 (0) 3/100 (3) 7/75 (9) ** 8/50 (16) ***
Lung, all tumors (adenocarcinoma, adenoma, epidermoid carcinoma)	0 250 500 1000	1/100 (1) 23/100 (23) *** 28/75 (37) *** 35/50 (70) ***	0 125 250 500	0/100 (0) 6/100 (6) ** 11/75 (15) *** 13/50 (26) ***
Mammary, adenocarcinoma	0 250 500 1000	1/100 (1) 5/100 (5) 8/75 (11) ** 14/50 (28) ***	0 125 250 500	0/100 (0) 1/100 (1) 3/75 (4) 3/50 (6) *
Zymbal gland, carcinoma	0 250 500 1000	1/100 (1) 8/100 (8) * 5/75 (7) 11/50 (22) ***	0 125 250 500	0/100 (0) 0/100 (0) 4/75 (5) * 6/50 (12) ***
Liver, hepatocellular carcinoma	0 250 500 1000	0/100 (0) 3/100 (3) 3/75 (4) 18/50 (36) ***	0 125 250 500	0/100 (0) 0/100 (0) 0/75 (0) 9/50 (18) ***
Hemangiosarcoma	0 250 500 1000	2/100 (2) 4/100 (4) 3/75 (4) 0/50 (0)	0 125 250 500	1/100 (1) 2/100 (2) 4/75 (5) 4/50 (8) *
Total Neoplasms[1]	0 250 500 1000	58/100 (58) 80/100 (80) *** 61/75 (81) *** 48/50 (96) ***	0 125 250 500	37/100 (37) 34/100 (34) 40/75 (53) * 36/50 (72) ***

* Significantly different from controls ($p<0.05$)
** Significantly different from controls ($p<0.01$)
*** Significantly different from controls ($p<0.001$)

[1] Includes rats with multiple neoplasms and neoplasms in other organs

At 18 months, survival in treated rats (80%) was slightly less than controls (96%), while at 20-22 months, survival was 55% in all groups (Russfield et al., 1975). Food consumption during the first 20-25 weeks of the study was similar in treated and control rats, but body weights at the end of the 18-month treatment period were reduced by about 100 g (13%) in the high-dose group and 50 g (7.5%) in the low-dose group. Body weights remained depressed throughout the 6-month recovery period. The study authors reported that no striking differences were seen in the incidence or intensity of gross or microscopic nonneoplastic lesions (data not shown). No statistically significant increases in tumor incidence were seen in treated rats, but there was some evidence for a tumorigenic effect from small increases in lung tumors (particularly adenomatosis, characterized as a metaplastic transformation of alveolar cells) and liver tumors (described as hepatomas) (Table 2). In mice, the high dose produced an increase in early mortality in females (data not shown). The low dose had no effect on survival in mice, and neither dose had any effect on food consumption or body weight in the mice. Incidence and intensity of nonneoplastic lesions were similar in treated and control mice (data not shown). There was a statistically significant increase in the incidence of liver tumors (hepatomas) in female mice of both dose groups (Table 2). Hepatomas were not increased in male mice. Slight increases in the incidences of vascular tumors (primarily subcutaneous hemangiomas and hemangiosarcomas) in both male and female mice were not statistically significant and were within the range of historical controls.

Stula et al. (1977) administered MOCA (90% pure) in gelatin capsules at 100 mg/day to 6 female purebred beagle dogs, 3 days per week for 6 weeks and then 5 days per week thereafter for up to 9 years. The average dose per treatment was 10.3 mg/kg and the average daily dose was 7.3 mg/kg-day, calculated from data provided by the investigators. Six control dogs received no treatment. Body weights were determined weekly. Hematology (erythrocyte count, hemoglobin concentration, hematocrit, total leukocyte count, and differential leukocyte), clinical chemistry (glucose, urea nitrogen, cholesterol, alkaline phosphatase, alanine aminotransferase (ALT), total protein, albumin-globulin ratio, and gamma-glutamyl transpeptidase), and urinalysis (volume, pH, appearance, osmolality, protein, sugar, blood, acetone, urobilinogen, bilirubin, and microscopic examination of the sediment [in addition to a yearly urine sediment cytology examination]) evaluations were performed throughout the study (approximately every 3 to 12 months). After approximately 8 to 9 years of treatment, surviving dogs were sacrificed by electrocution and necropsied. Twenty-seven tissues and all gross lesions were microscopically examined. There were no apparent treatment-related effects on mortality (1 treated dog died after 3.4 years on study due to natural causes unrelated to MOCA ingestion) or body weights. Mean serum ALT was statistically significantly increased by over 2-fold in the treated dogs (a control dog that had consistently high ALT measurements throughout the study, later found to be associated with marked cholangiofibrosis of the liver in this individual, was excluded from this analysis). After 7 years on study, urine sediment changes (increased erythrocytes, leukocytes, epithelial cells - some with abnormalities) suggested development of tumors in the genitourinary tract in treated dogs. Subsequent examinations revealed that 4 of the 5 treated dogs surviving 8-9

Table 2. Tumor Incidence in Male and Female Test Animals Exposed to MOCA Hydrochloride Salt in the Diet for 18 Months (Russfield et al., 1975)[a]

	Incidence (%)			
Tumor	0 ppm	500 ppm	1000 ppm	2000 ppm
Male Rats				
Lung, Adenomatosis	0/22 (0)	3/22 (14)	4/19 (21)	n/a
Lung, Adenoma	1/22 (4)	1/22 (4)	1/19 (5)	n/a
Lung, Adenocarcinoma	0/22 (0)	1/22 (4)	1/19 (5)	n/a
Liver, Hepatoma	0/22 (0)	1/22 (4)	4/19 (21)	n/a
Male Mice				
Liver, Hepatoma	3/18 (17)	n/a	3/13 (23)	4/20 (20)
Vascular, Hemangioma	0/18 (0)	n/a	2/13 (15)	5/20 (25)
Vascular, Hemangiosarcoma	0/18 (0)	n/a	1/13 (8)	3/20 (15)
Female Mice				
Liver, Hepatoma	0/20 (0)	n/a	9/21 (43) **	7/14 (50) **
Vascular, Hemangioma	1/20 (5)	n/a	0/21 (0)	4/14 (29)
Vascular, Hemangiosarcoma	0/20 (0)	n/a	0/21 (0)	2/14 (14)

[a] Concentration of the HCl salt is reported in this table
** Significantly greater than controls ($p<0.01$)
n/a = not applicable

years had papillary transitional cell carcinomas of the urinary bladder, a statistically significant increase over the 0/6 incidence of this tumor in controls. The other treated dog had a combined transitional cell carcinoma and adenocarcinoma of the urethra. Follicular cystitis (slight in severity), seen in the bladders of all treated dogs that survived 8-9 years, was often found adjacent to a tumor. This lesion was not seen in control dogs. Nodular hyperplasia of the liver was observed in 3/5 treated dogs that survived 8-9 years, which was a statistically significant increase over controls (0/6).

No studies evaluating the toxicity of MOCA via inhalation exposure are available.

Other Studies

MOCA has been extensively tested for genotoxicity. Results have been summarized by U.S. EPA (1990), ATSDR (1994), and IARC (1993). MOCA was generally positive in tests for reverse mutation in *Salmonella typhimurium* TA98 and TA100 with metabolic activation, but not without activation or in other tester strains. Results were mixed for reverse mutation in *Escherichia coli* with activation and negative without. Tests for prophage induction in *E. coli* (with activation) and differential toxicity in *Bacillus subtilus* (with or without activation) were positive. In the yeast *Saccharomyces cerevisiae,* MOCA produced positive results in an assay for aneuploidy (without activation), but mixed or negative results in assays for gene conversion, reverse mutation, and homozygosis. *In vitro* tests in mammalian cells were positive for forward mutation in mouse lymphoma cells (with activation, but not without), unscheduled DNA synthesis in rat, mouse, and hamster primary hepatocytes (without activation), single strand DNA breaks in hamster and human lung embryonic cells (without activation), DNA adduct formation in dog and human bladder explant culture (without activation), and cell transformation in BALB/c 3T3 mouse cells, RLV/Fischer rat embryo cells, and Syrian hamster kidney BAK cells (with or without activation). Results were equivocal or negative for sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells and human leukocytes *in vitro* (with or without activation). *In vivo* assays for mutations in *Drosophila melanogaster*, micro nucleus formation in mice, and covalent binding to DNA in rat lung, liver, and kidney were all positive. These results show that MOCA is a genetic toxicant with a broad range of activity. The requirement for activation in most *in vitro* assays suggests that a metabolite is the proximate genetic toxicant.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 4,4'-METHYLENEBIS(2-CHLOROANILINE)

Limited human studies found no noncancer effects attributable to MOCA, but were primarily interested in cancer effects. Animal studies for MOCA were designed primarily as cancer studies, but observations regarding nonneoplastic effects were reported in some of them.

For example, the liver was identified as a target of MOCA toxicity in chronically exposed rats and dogs. Stula et al. (1975) reported nonneoplastic liver lesions, including hepatocytomegaly, fatty change, necrosis, bile duct proliferation, and fibrosis, in male and female Charles River CD rats fed a diet containing 1000 ppm (50 mg/kg-day) of MOCA for up to two years. Liver tumors were also seen in some rats in the treated group. Details regarding the incidence and severity of the nonneoplastic lesions were not reported. The wording of the paper suggests that the liver lesions accompanied the liver tumors, but it is not clear whether they were also seen in animals without tumors. The researchers reported that occurrence of nonneoplastic liver lesions was similar in a second experiment using a protein-restricted diet, although liver tumor incidence in male rats was significantly increased under these conditions.

Other studies in rats and mice (Kommineni et al., 1978; Ruchfield et al., 1975) treated with 12.5 to 50 mg/kg-day of MOCA in the diet for 18 months did not provide any evaluation of non-neoplastic effects. Both of these studies included a 6-month recovery period after treatment, which would have made detection of nonneoplastic lesions difficult, as treatment-related lesions might have been repaired and/or obscured by age-related changes during this time. The 9-year dog study found an over 2-fold increase in mean serum ALT in treated dogs versus controls, and a statistically significant increase in nodular hyperplasia of the liver in the treated dogs (3/5, versus 0/6 in controls). No liver tumors were found in the dogs. The average daily dose of MOCA in the treated dogs was 7.3 mg/kg-day. These studies establish that the liver is a sensitive target of toxicity for MOCA. The lowest dose known to produce an effect on the liver is 7.3 mg/kg-day in the 9-year dog study. A NOAEL has not been established.

A provisional **chronic RfD of 0.002 mg/kg-day** (2E-3) can be derived for MOCA from the dog LOAEL of 7.3 mg/kg-day by applying an uncertainty factor of 3000 (10 for use of a LOAEL, 10 to extrapolate from dogs to humans, 10 to protect sensitive individuals, and 3 for database deficiencies, including lack of reproductive or developmental toxicity studies), as follows:

$$\begin{aligned} \text{p-RfD} &= \text{LOAEL} \div \text{UF} \\ &= 7.3 \text{ mg/kg-day} \div 3000 \\ &= 0.002 \text{ mg/kg-day or } 2\text{E-}3 \text{ mg/kg-day} \end{aligned}$$

In the absence of any subchronic oral data, the chronic p-RfD of 0.002 mg/kg-day can be adopted as a protective estimate of the subchronic p-RfD, leading to a provisional **subchronic RfD of 0.002 mg/kg-day** for MOCA.

Confidence in the key study is low. The study included only a small number of dogs of one sex, and only one dose level was tested. Confidence in the database is low; as reproductive and developmental toxicity have not been studied, and systemic toxicity data are available only

from studies designed primarily as cancer bioassays that failed to identify a NOAEL. Low confidence in the subchronic and chronic p-RfD values follows.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 4,4'-METHYLENEBIS(2-CHLOROANILINE)

Limited human studies found no noncancer effects attributable to MOCA, but were primarily interested in cancer effects. No animal data regarding the toxicity of MOCA following subchronic or chronic inhalation exposure are available. Therefore, derivation of subchronic and chronic p-RfC values for MOCA is precluded.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 4,4'-METHYLENEBIS(2-CHLOROANILINE) (MOCA)

Weight-of-Evidence Classification

Human data are not adequate for carcinogenicity evaluation of MOCA, although there is suggestive evidence that MOCA may produce bladder tumors in humans. Animal data have consistently shown that MOCA is carcinogenic in all laboratory animal species evaluated (rats, mice, and dogs). Tumor production has occurred at the lowest dose evaluated in all species, and the available data suggest that MOCA is comprehensively genotoxic. According to the 2005 Cancer Guidelines, the descriptor "Likely to be carcinogenic to humans" is appropriate for MOCA. This descriptor is applied when "...the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans". MOCA satisfies at least two of the illustrative examples described under this category including, "...an agent demonstrating a plausible (but not definitely causal) association between human exposure and cancer..." and "... an agent that has tested positive in animal experiments in more than one species, sex, strain, or exposure route, with or without evidence of carcinogenicity in humans". Suggestive epidemiologic evidence is available and MOCA has tested positive in rats, mice, and dogs in adequate studies. IARC classified MOCA as "probably carcinogenic to humans."

Quantitative Estimates of Carcinogenic Risk

Dose-response modeling for MOCA was conducted on data from the studies of Kommineni et al. (1978) in male rats (protein-adequate study only) and Russfield et al. (1975) in female mice. Each of these studies included multiple dose levels and reported statistically significant increases in at least one tumor type. Both were adequate cancer bioassays, although group sizes were small in the Russfield et al. (1975) study. While it is technically possible to

model the results of a single-dose study (e.g., the rat study of Stula et al., 1975 or the dog study of Stula et al., 1977), such studies provide little information about the shape of the dose-response curve, limiting their utility for dose-response modeling.

A weight of evidence evaluation supports a determination that MOCA is carcinogenic by a mutagenic MOA. Determination of the mode of action of carcinogens is addressed in Section 5 of the 2005 Cancer Supplementary Guidance (U.S. EPA, 2005b) as follows: "Determinations of chemicals that are operating by a mutagenic mode of action entails evaluation of test results for genotoxic endpoints, metabolic profiles, physiochemical properties, and structure-activity relationships (Waters et al., 1999)." These factors are considered below:

Genetic endpoints: As described in the previous section entitled "Other Studies" short term tests results provide ample evidence for mutagenicity (heritable genetic damage). Positive tests include bacteria (Ames test), yeast, *in vitro* mammalian cells for forward mutation in mouse lymphoma cells, unscheduled DNA synthesis in rat, mouse and hamster primary hepatocytes, single strand DNA breaks in hamster and human lung embryonic cells, DNA adduct formation in dog and human bladder explant culture, and cell transformation BALB/c 3T3 mouse cells, RLV/Fisher rat embryo cells, and Syrian hamster kidney BK cells. *In vivo* assays in *Drosophila melanogaster*, micro nucleus in mice and covalent binding to DNA in rat lung, liver and kidney were also positive. Metabolic activation was required in many tests indicating a metabolite is necessary for the action. Other mechanisms of carcinogenesis are possible in addition to mutagenesis, e.g. mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, immune suppression, interference with repair enzymes or genes, oxidative damage, etc.

Metabolic profiles: Metabolic activation was required in many of the genotoxicity tests, indicating that a metabolite, rather than the parent compound, is the proximate carcinogen. There is no data to support a unique metabolic profile in humans.

Physiochemical properties: There are no properties that would suggest significant differences in absorption, distribution, elimination in humans vs. non-human animals to the extent that the proximate carcinogen would not be available at the target organ(s).

Structure-activity analyses in a weight of evidence approach: MOCA is structurally similar to benzidine, a known human bladder carcinogen. Benzidine is known to produce various tumor types at multiple sites in animal species exposed by several routes and is positive in Ames test, mouse lymphoma, DNA damage assays, sister chromatid exchange, and micronucleus formation. The structural and toxicological similarity of MOCA to benzidine supports selection of a mutagenic MOA for the carcinogenic action of MOCA. This p-SF for MOCA is based on lung tumors, however, mammary, zymbal gland, liver tumors, and hemangiosarcomas and also bladder cancer were observed in supporting studies. According to the 2005 Cancer Guidelines,

concordance of tumor sites is not required for supporting evidence. The lung tumors provide the most sensitive endpoint in these studies.

The mode of action evidence for MOCA is analyzed under the mode of action framework in EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a, Section 2.4.3).

1. MOA sufficiently supported in animals? The studies clearly show carcinogenesis in animals; short term testing clearly indicates a mutagenic mode of action in several cell types and tests, as indicated earlier.

2. MOA relevant to humans? MOCA is a systemic mutagen in test animals; Epidemiologic investigations are suggestive; a QSAR surrogate, benzidine, is carcinogenic to humans, likely by a mutagenic endpoint.

3. Susceptible lifestages or populations? This is discussed in the following pages in relation to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005b).

The hypothesis that MOCA carcinogenicity has a mutagenic mode of action is presumed to apply to all tumor types.

Dose response modeling was performed based on statistically significant tumors in the Kommineni et al. (1978) and Russfield et al. (1975) studies: lung adenocarcinomas and combined tumors, mammary adenocarcinomas, Zymbal gland carcinomas, and liver hepatocellular carcinomas in male rats (Table 3) and liver hepatomas in female mice (Table 4). The derivations used the U.S. EPA (2005) guidelines for cancer risk assessment. Since a mutagenic mode of action is appropriate for MOCA-induced tumors, the BMD multistage model was used for dose-response modeling. Background incidence was included as extra risk. In accordance with the 2005 Cancer guidelines, the $BMDL_{10}$ (95^{th} percentile lower bound on dose estimated to produce a 10% increase in tumor incidence over background) was estimated using the U.S. EPA (1996, 2000) benchmark dose methodology, and a linear extrapolation to the origin was performed by dividing the $BMDL_{10}$ into 0.1 (10%). The values based directly on the oral animal tumor data are adjusted to human values by correcting for differences in body weight between humans and rodents. U.S. EPA uses a cross-species scaling factor of body weight raised to the ¾ power (U.S. EPA, 2005). Adjustment from animal to human slope factor is performed by multiplying the animal value by the ratio of human to animal body weight raised to the ¼ power and by multiplying this product by the ratio of life span of animal to duration of the experiment raised to the 3^{rd} power. The latter term reduces to 1 for both of the studies being modeled since the 2-year duration of the studies (including the 6 month observation period) is equal to the reference life span of 24 months in rodents. The short exposure duration in both of

these studies (18 out of 24 months) is taken into account in calculation of the average daily doses used in the modeling exercises.

Data for each tumor grouping are shown in Tables 3,4 and 5. Slope factors estimated as $0.1/BMDL_{10}$ were very similar for each tumor grouping. The highest estimate of human cancer risk was based on the combined incidence of lung tumors (adenoma, adenocarcinoma, epidermoid carcinoma) in male rats (**human $0.1/BMDL_{10}$ = 0.10 per mg/kg-day, 1E-1 per mg/kg-day**) (rounded from 9.95E-2 - Table 3). Successively lower estimates, all within one order of magnitude of the high risk estimate, were derived from lung adenocarcinomas in male rats, liver hepatomas in female mice, mammary adenocarcinomas in male rats, Zymbal gland adenocarcinomas in male rats, and liver hepatocellular carcinomas in male rats. Figures (1-6) demonstrating the model fits are included at the end of this document.

EPA has concluded, by a weight of evidence evaluation, that MOCA is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (*Supplemental Guidance*) (U.S. EPA, 2005b) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for MOCA are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of 1E-1 per mg/kg-day, calculated from data from adult exposure, does not reflect presumed early-life susceptibility for this chemical and age-dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance* which establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The 10-fold and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to MOCA. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for MOCA, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The oral slope factor, calculated from adult exposure, is derived from the $BMDL_{10}$, the 95% lower bound on the exposure associated with an 10% extra cancer risk, by dividing the risk (as a fraction) by the $BMDL_{10}$, and represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to MOCA's mutagenic mode of action:

The slope of the linear extrapolation from the central estimate, human BMD_{10} is 0.1/(14.37 mg/kg-day) = 7E-3 per mg/kg-day. The BMD_{10} for humans was calculated from the BMD_{10} for animals according to the same procedure for conversion of the $BMDL_{10}$ for animals to humans.

The slope factor for MOCA should not be used with exposures exceeding the point of departure ($BMDL_{10}$) 1 mg/kg-day, because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of MOCA. For exposures greater than the $BMDL_{10}$, contact the Superfund Technical Support Center. Additionally, age-dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks to individuals <16 years old as discussed above (U.S. EPA, 2005).

There are no suitable human or animal carcinogenicity data from which to derive a provisional inhalation unit risk for MOCA.

Table 3. BMD_{10}, BMDL Values Based on Lung, Mammary, Zymbal Gland, and Liver Tumor Incidences in Male Rats (Kommineni et al., 1978)

Tumor	Average Daily Dose (mg/kg-day)[1]				rat BMD_{10}	rat $BMDL_{10}$	rat[2] $0.1/BMDL_{10}$	Human[3] $0.1/BMDL_{10}$ OSF
	0	9.4	18.8	37.5				
Lung (adenoma, epidermoid carcinoma, adenocarcinoma)	1/100	23/100	28/75	35/50	4.45	3.25	3.08E-2	9.95E-2
Lung (adenocarcinoma)	0/100	14/100	20/75	31/50	7.45	5.01	1.96E-2	6.34E-2
Mammary (adenocarcinoma)	1/100	5/100	8/75	14/50	18.70	12.83	7.80E-3	2.52E-2
Zymbal gland (adenocarcinoma)	1/100	8/100	5/75	11/50	19.66	13.32	5.96E-3	2.43E-2
Liver (hepatocellular carcinoma)	0/100	3/100	3/75	18/50	20.03	16.78	6.42E-3	1.93E-2

[1]Rats were exposed to dietary levels of 0, 250, 500, or 1000 ppm of MOCA for 18 months and observed for an additional 6 months. Doses of 0, 12.5, 25, and 50 mg/kg-day were estimated by assuming that a rat consumes 5% of his body weight per day. These doses were expanded to continuous exposure by multiplying by 18/24 months.

[2]Rat $BMDL_{10}$ values were calculated (extra risk, background estimated in model) from the lowest-degree polynomial model that gave an adequate fit (chi-square goodness-of-fit statistic p value >0.05), as per the U.S. EPA (1996) Benchmark Dose Technical Guidance Document. Models with more than 2 parameters were not considered for selection (degrees of freedom = # dose groups -2 = 4-2 = 2).

[3]Human value calculated as: rat value ($0.1/BMDL_{10}$) x $(W_{hum} / W_{rat})^{1/4}$ x $(L / L_e)^3$ where W_{hum} = 70 kg (human reference body weight), W_{rat} = 0.64 kg (TWA male rat body weight for the lowest affected dose group during the 18 month exposure), L = 24 months (rat life span), L_e = 24 months (duration of experiment)

Table 4. BMD_{10}, BMDL Values Based on Liver Tumor Incidence in Female Mice (Russfield et al., 1975)

Tumor	Dose (mg/kg-day)[1]			mouse BMD_{10} mg/kg-day	mouse[2] $BMDL_{10}$ mg/kg-day	mouse $0.1/BMDL_{10}$ mg/kg-day	human $0.1/BMDL_{10}$[3] $(mg/kg\text{-}day)^{-1}$ OSF
	0	97	194				
Liver (hepatoma)	0/20	9/21	7/14	23.09	15.58	6.42E-3	4.28E-2

[1]Mice were exposed to dietary levels of 0, 1000, or 2000 ppm of MOCA hydrochloride salt for 18 months and observed for an additional 6 months. Doses of 0, 129.5, and 259 mg/kg-day were estimated by assuming that a mouse consumes 15% of his body weight per day and adjusting for MOCA content of the administered material based on molecular weight. These doses were expanded to continuous exposure by multiplying by 18/24 months.

[2]Mouse $BMDL_{10}$ calculated (extra risk, background estimated in model) from the lowest-degree polynomial model that gave an adequate fit (chi-square goodness-of-fit statistic p value >0.05), as per the U.S. EPA (1996) Benchmark Dose Technical Guidance Document. A 2-degree polynomial model was chosen.

[3]Human value $0.1/BMDL_{10}$) calculated as: mouse value ($0.1/BMDL_{10}$) x $(W_{hum} / W_{mouse})^{1/4}$ x $(L / L_e)^3$ where W_{hum} = 70 kg (human reference body weight), W_{mouse} = 0.0353 kg (U.S. EPA, 1988 reference value), L = 24 months (rat life span), L_e = 24 months (duration of experiment)

Table 5. BMD results

Tumor Groups	BMD_{10} (animal) mg/kg-day	$BMDL_{10}$ (animal) mg/kg-day	$0.1/BMDL_{10}$ (animal) $(mg/kg\text{-}day)^{-1}$	Probability	human $0.1/BMDL_{10}$ $(mg/kg\text{-}day)^{-1}$ OSF
Rat Lung: adenoma, epidermoid carcinoma, adenocarcinoma	4.47	3.25	3.08E-2	0.528	9.95E-2
Rat Lung: adenocarcinoma	7.45	5.10	1.96E-2	0.875	6.34E-2
Mouse Liver	23.09	15.58	6.42E-2	0.637	4.28E-2
Rat Mammary	18.70	12.73	7.80E-2	0.920	2..52E-2
Rat Zymbal	19.66	13.32	7.50E-3	0.139	2.43E-2
Rat Liver	20.03	16.77	5.96E-3	0.390	1.93E-2

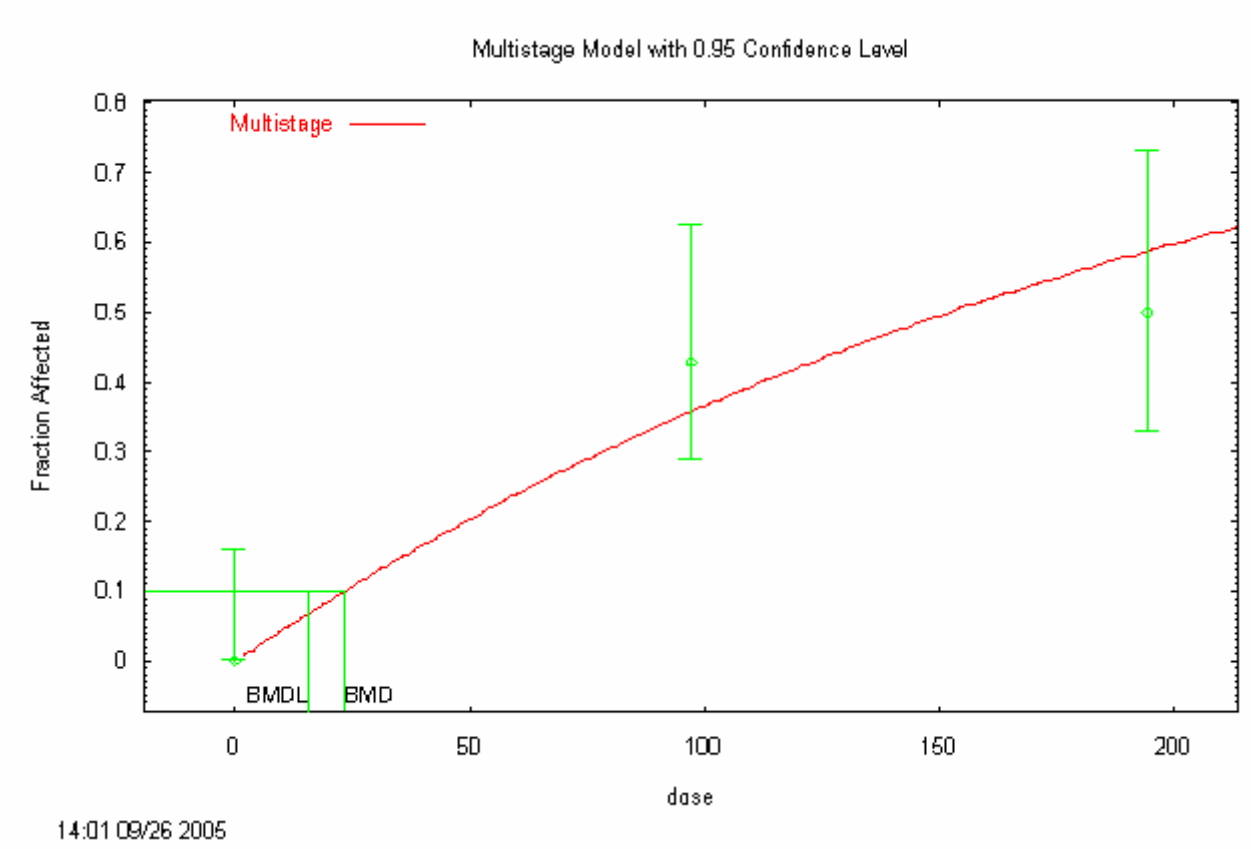

Figure 1: Lung: adenoma, epidermoid carcinoma, adenocarcinoma (units in abscissa are mg/kg-day)

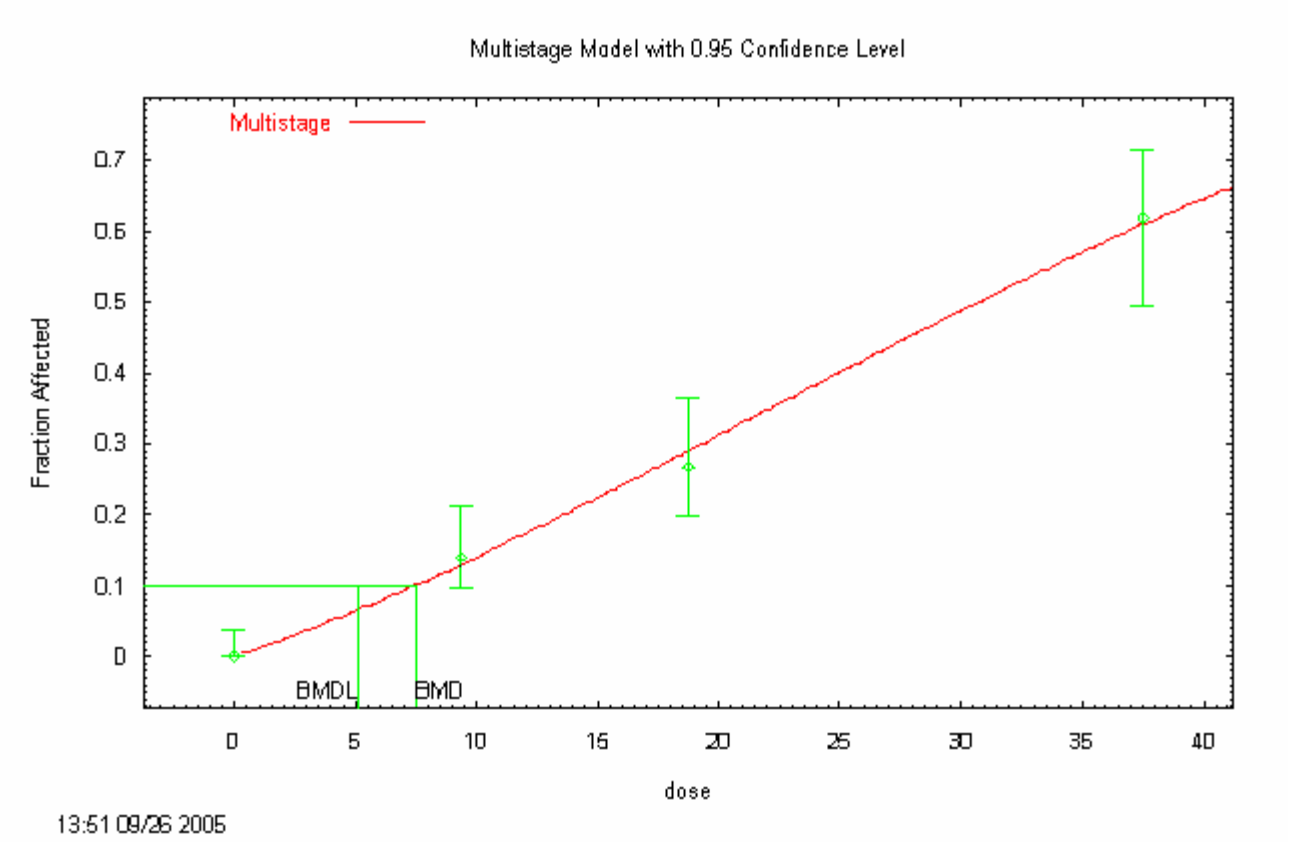

Figure 2: Lung (adenocarcinoma) (units in abscissa are mg/kg-day)

Figure 3: Mammary (adenocarcinoma) (units in abscissa are mg/kg-day)

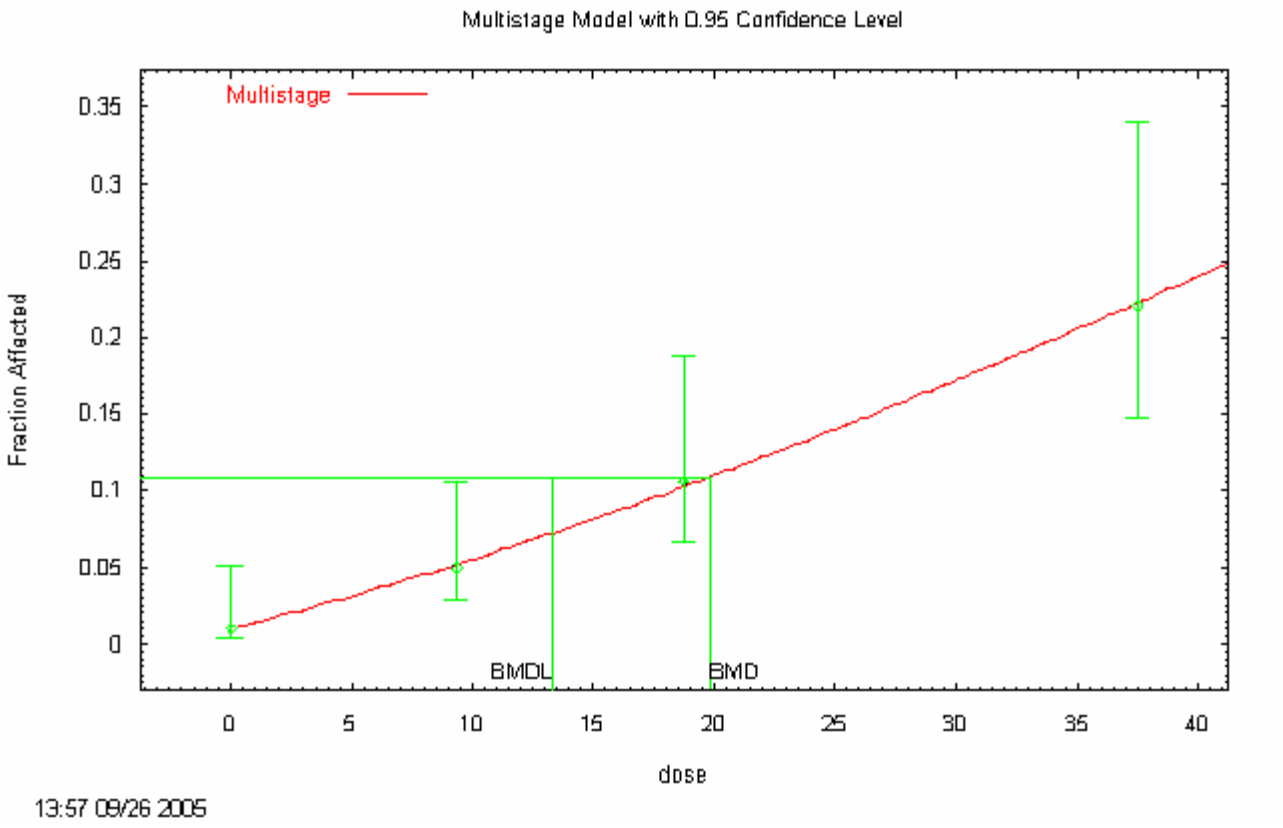

Figure 4: Zymbal Gland (units in abscissa are mg/kg-day)

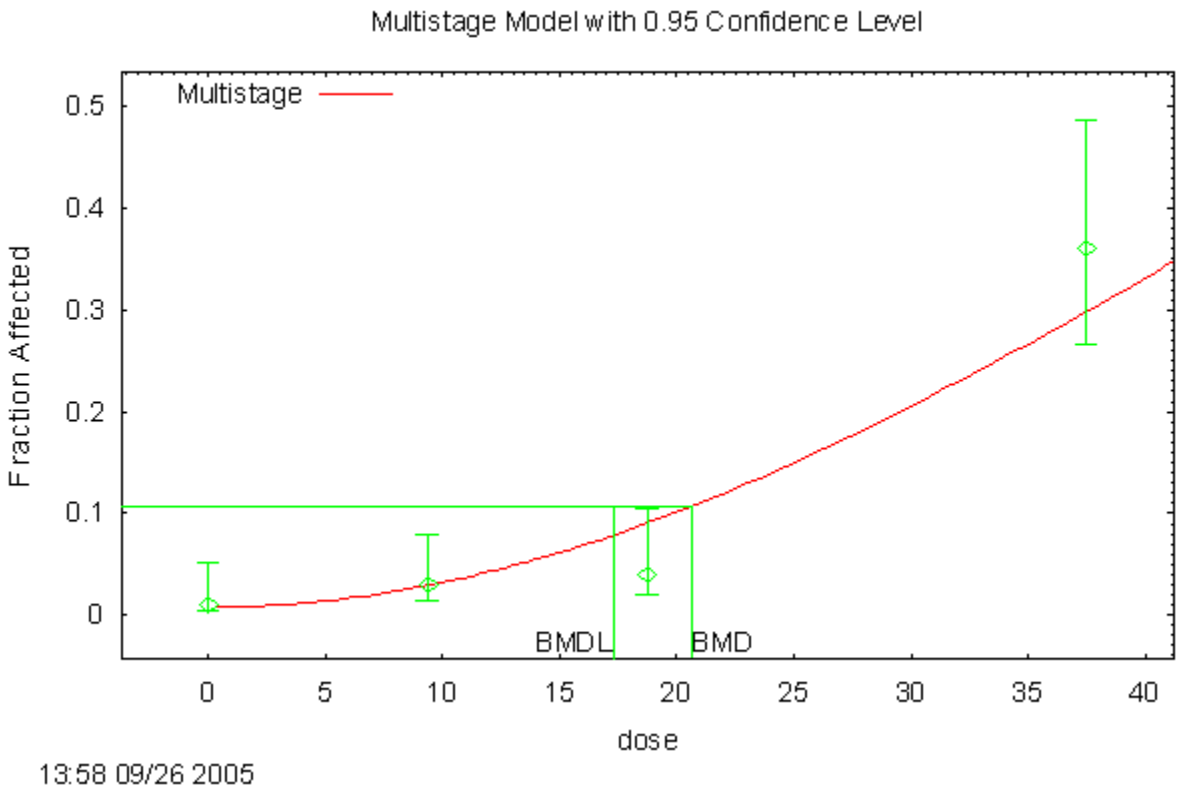

Figure 5: Liver: hepatocellular carcinoma (units in abscissa are mg/kg-day)

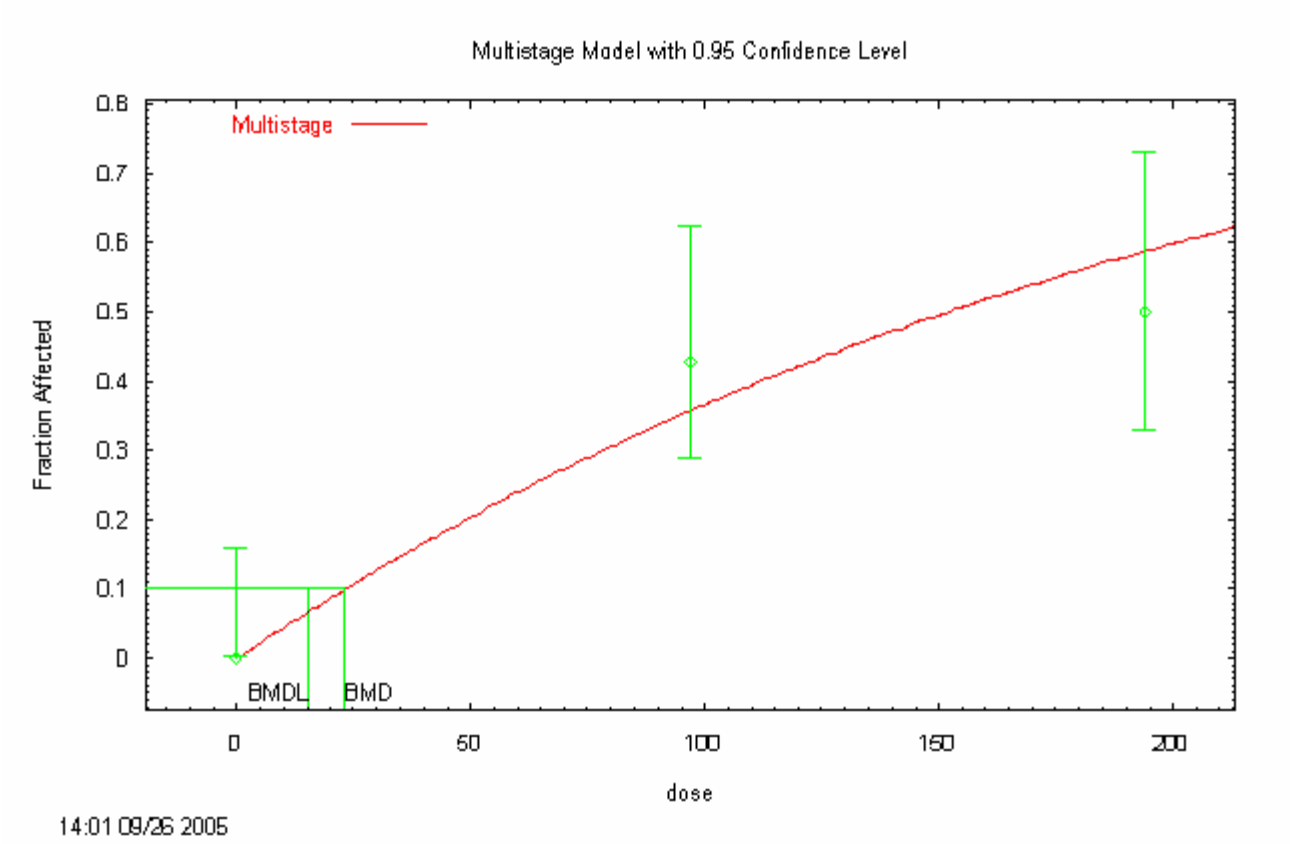

Figure 6: Liver, Hepatoma (Russfeld et al., 1975) (units in abscissa are mg/kg-day)

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