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## Chronic Dermal Toxicity of Epoxy Resins

### I. Skin Carcinogenic Potency and General Toxicity

J. M. Holland  
L. C. Gipson  
M. J. Whitaker  
B. M. Eisenhower  
T. J. Stephens

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BIOLOGY DIVISION

CHRONIC DERMAL TOXICITY OF EPOXY RESINS

I. SKIN CARCINOGENIC POTENCY AND GENERAL TOXICITY

J. M. Holland, L. C. Gipson, M. J. Whitaker, B. M. Eisenhower,  
and T. J. Stephens

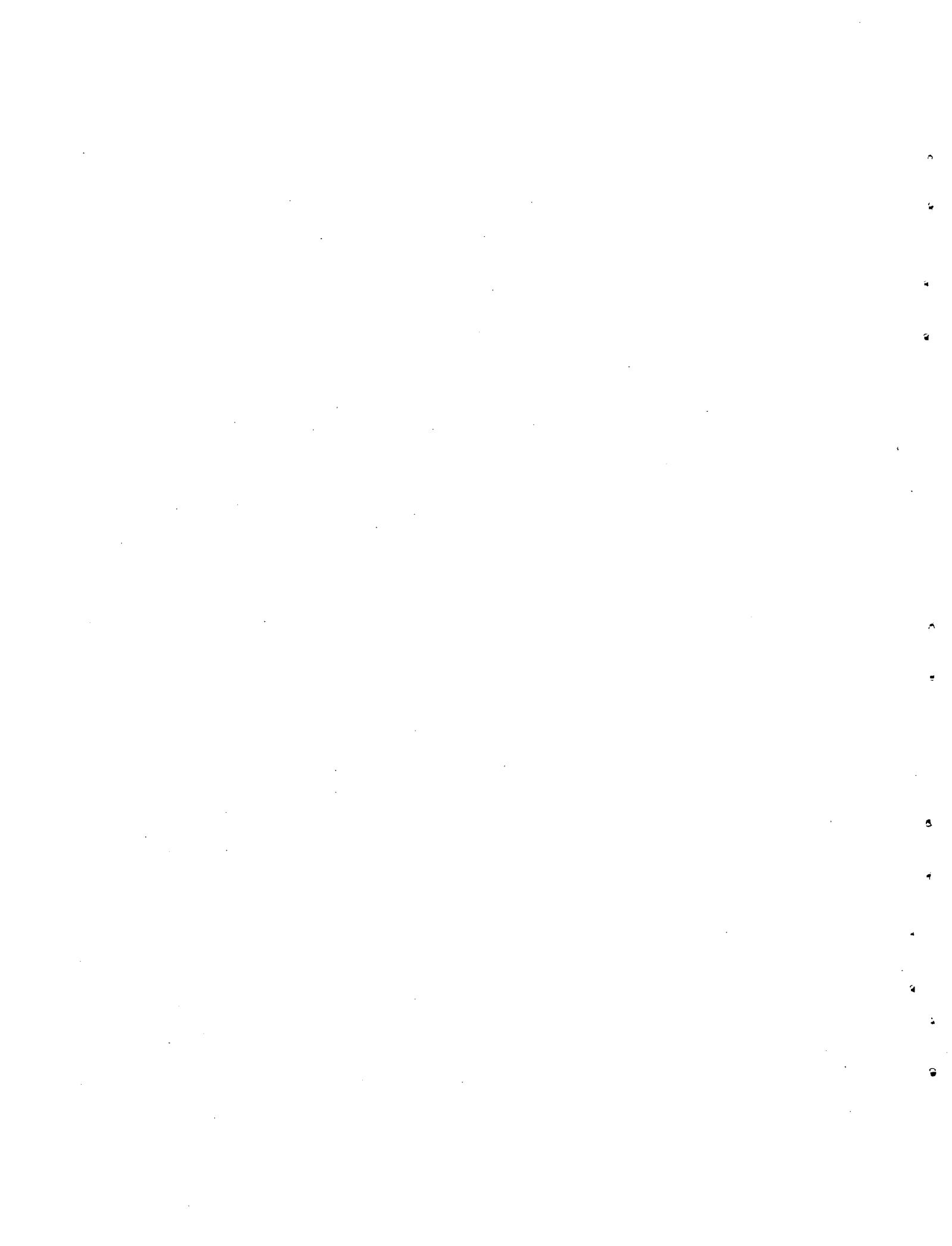
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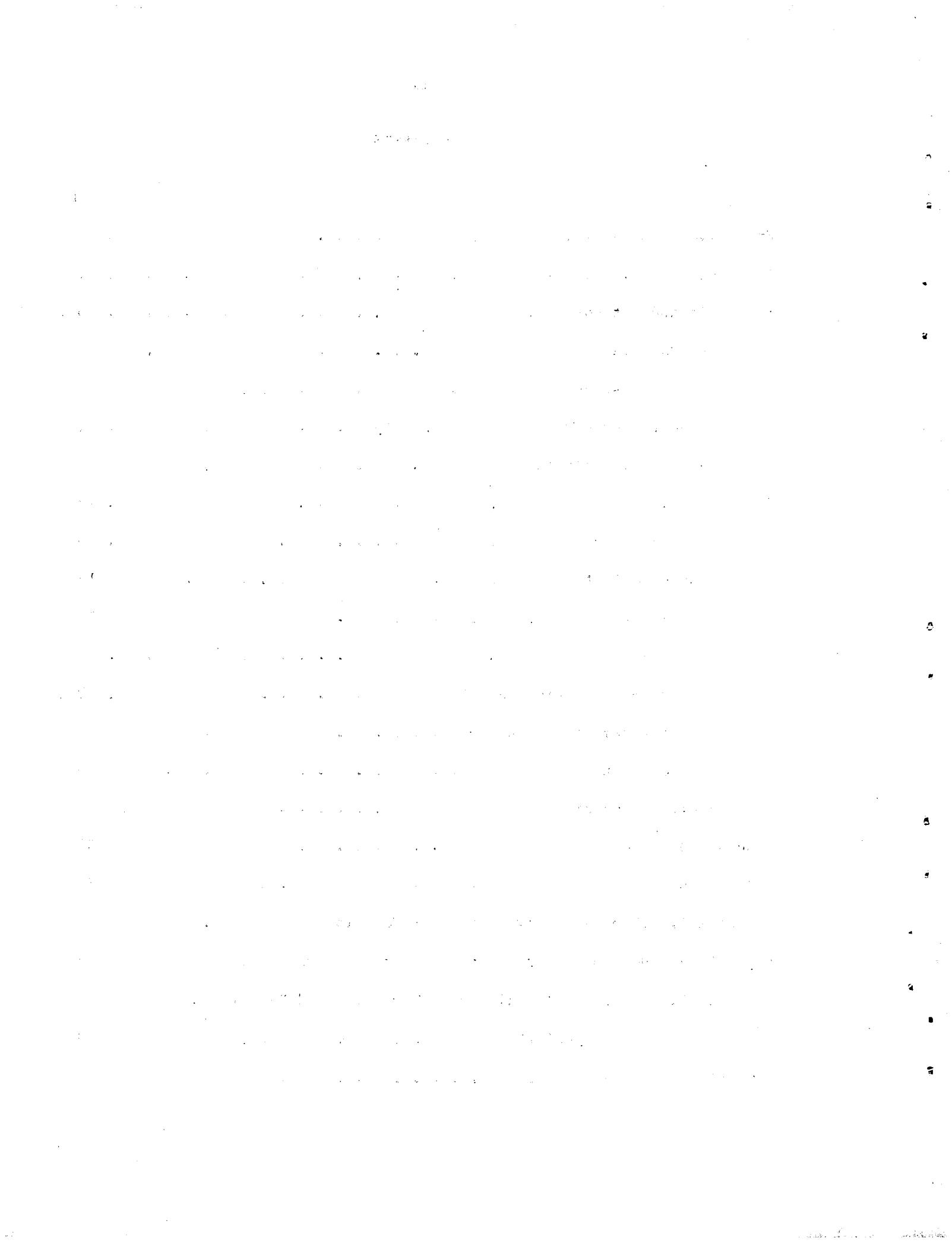


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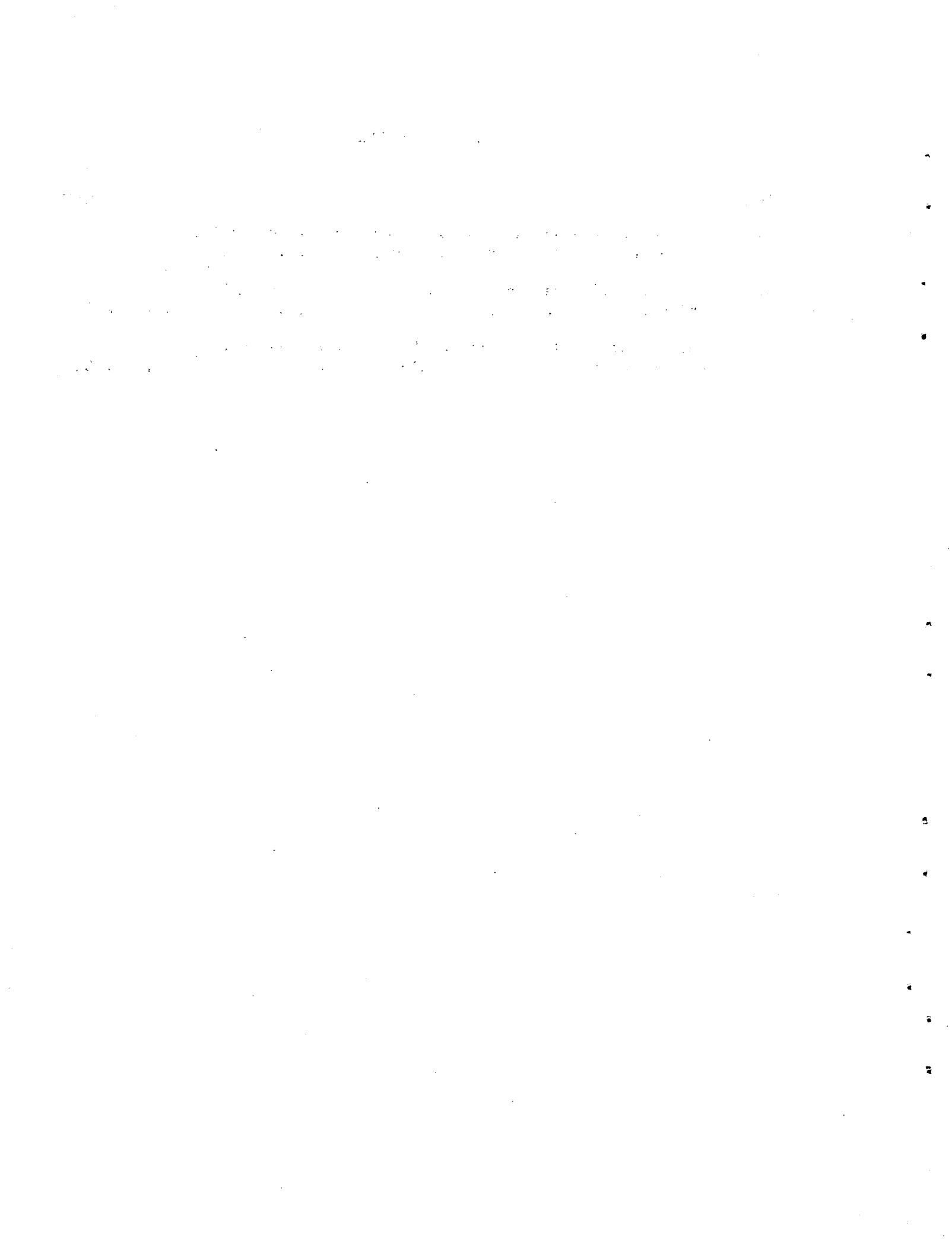
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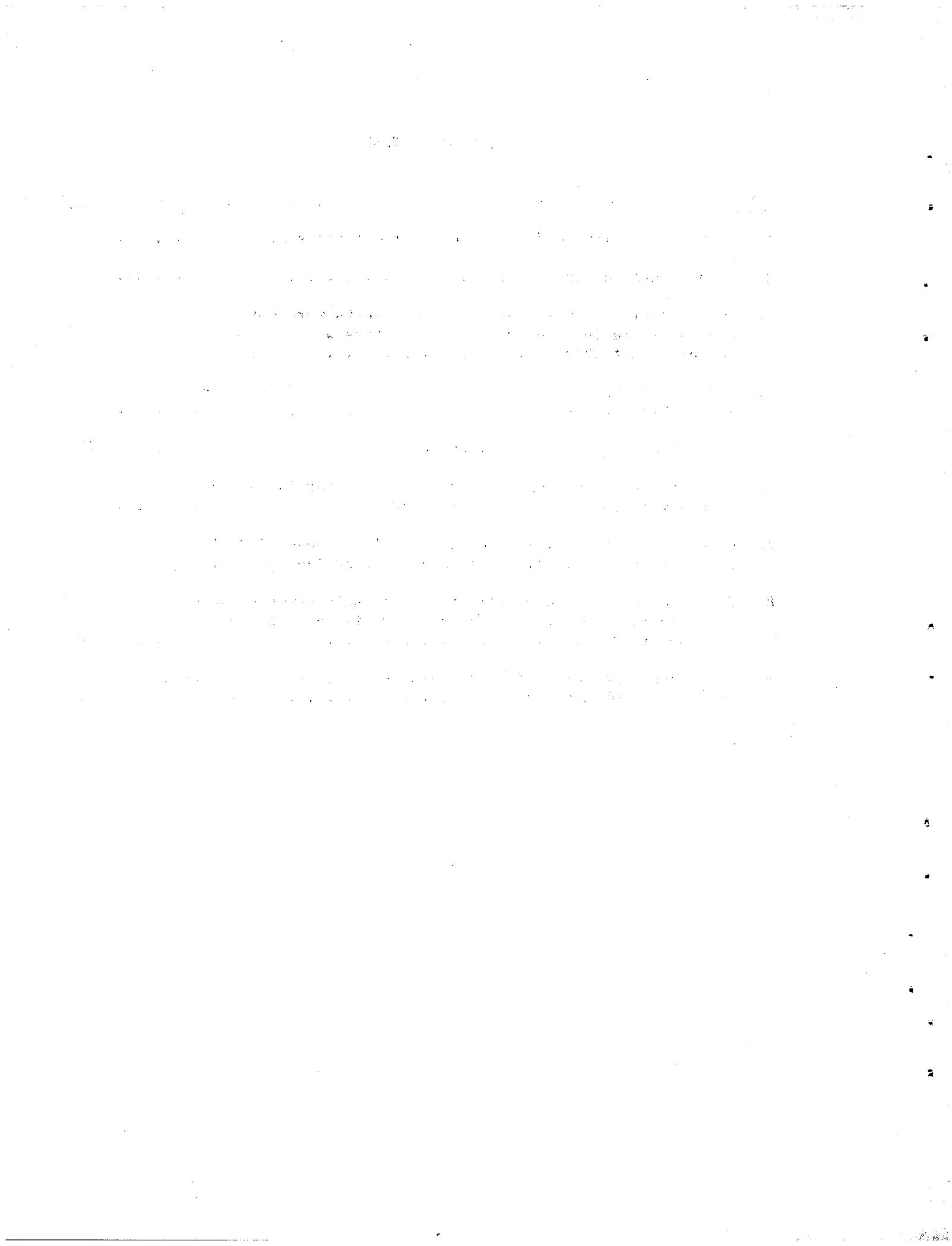
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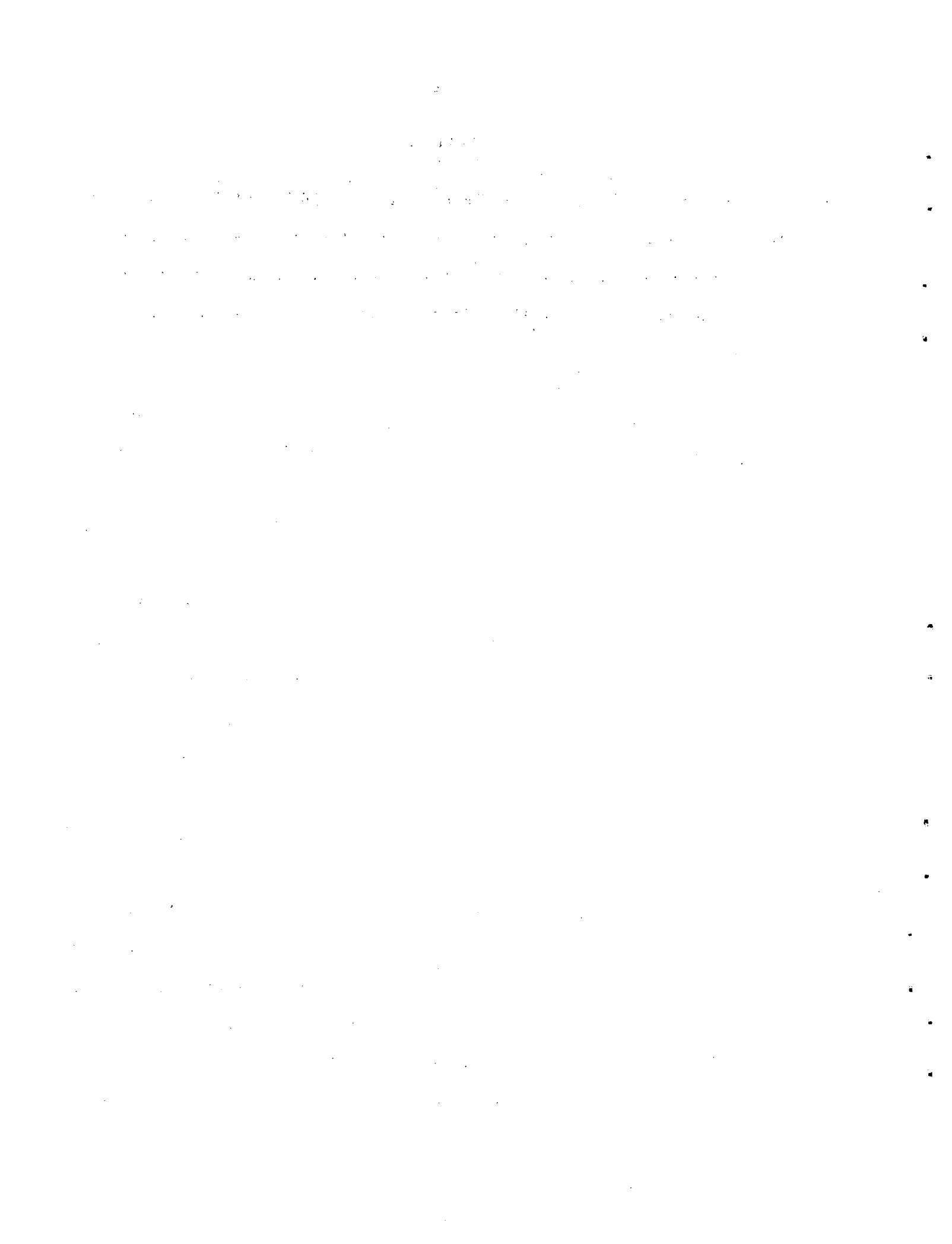
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CHRONIC DERMAL TOXICITY OF EPOXY RESINSI. SKIN CARCINOGENIC POTENCY AND GENERAL TOXICITY

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and T. J. Stephens

#### EXECUTIVE SUMMARY

This report describes and quantifies the cutaneous and systemic response of male and female C3H mice to skin application of selected commercial epoxy resins and amine curing agents, at the maximum tolerated dermal dose (MTDD). Relevant findings were:

- (1) At 75 mg per week, diglycidyl ether of bisphenol A (DGEBA) (CAS no. 1675-54-3), obtained from three separate manufacturers, accelerated mortality in female but not in male mice, had no effect on body weight in either sex, and had no effect on hematological or clinical chemical parameters. Skin exposed to this material exhibited hyperkeratosis, alopecia, depigmentation and sporadic focal inflammation. Treatment-related skin neoplasms were not observed under the prevailing test conditions.
- (2) Equal-parts mixtures of the same resins with bis(2,3-epoxycyclopentyl) ether (CAS no. 2386-90-5), a resin shown previously to be a weak skin carcinogen in strain C3H, resulted in positive synergism; the activity of the combination exceeded, by a substantial margin, the activity of either component applied separately. Elevated white cell counts were noted but were considered secondary to cutaneous neoplasms. Skin carcinogenic potencies, relative to benzo(a)pyrene [B(a)P], were similar for all three DGEBA combinations and varied with dose rate,

from approximately 1/5,000th to 1/20,000th the activity of an equivalent surface dose of B(a)P.

- (3) A DGEBA manufactured by Union Carbide Corporation (Material E, Appendix A) in the mid-1970's and assayed for skin carcinogenicity previously was chemically characterized. The results of this analysis are included with the present data for comparison purposes.
- (4) The corrosiveness of diglycidyl ether of resorcinol (CAS no. 101-90-6) limited the MTDD to 1.8 mg/week. At this dose, systemic toxicity was noted which included weight loss, early and accelerated mortality, and dose-related reduction in white cell count and blood glucose relative to age- and sex-matched vehicle controls. Skin changes included mild hyperkeratosis, depigmentation, and follicle depletion. Treatment-related skin neoplasms were not observed at any dose.
- (5) N,N'-diglycidyl-5,5-dimethylhydantoin (CAS no. 15336-81-9) was also a potent direct skin irritant which limited the MTDD to 3.75 mg/week. At this dose level there was accelerated mortality in female but not in male mice and no effect on body weight or clinical parameters. This material was found to be a moderately potent skin carcinogen with an activity approximately 1/200th that of B(a)P.
- (6) The diglycidyl ether of neopentyl glycol (CAS no. 17557-23-2) was a potent skin irritant which limited the MTDD to 3.75 mg/week. At this dose level there was no effect on average body weight in either sex. An increased mortality at a single intermediate dose level in female mice was noted. The material was carcinogenic in skin of both sexes with a potency approximately 1/700th that of B(a)P.

- (7) A 70:30 mixture of the hydantoin and neopentyl glycol base resins, respectively, applied at the MTDD of 3.75 mg/week reflected the same pattern of systemic toxicity and skin carcinogenicity observed with each component separately, thus there was no indication of synergism between these materials. The skin tumorigenic potency of the combination was approximately 1/200th that of B(a)P, which is similar to the activity of the hydantoin base resin alone.
- (8) The amine curing agent methane diamine (CAS no. 80-52-4) was a potent skin irritant. In mice exposed at the MTDD of 3 mg/week, body weight, overall mortality, blood count, and blood chemistry values were not significantly different from those in age- and sex-matched vehicle controls. This material induced mild thickening and scaling of the skin and depletion of hair follicles. Treatment-related skin tumors were not induced.
- (9) A second curing agent consisting of an eutectic mixture of meta-phenylenediamine (CAS no. 108-45-2) and DGEBA was systemically toxic via percutaneous absorption. This limited the MTDD to 9 mg/week. At this dose level there was a significantly increased mortality in mice of both sexes. Blood counts, blood chemistry, and body weights were not affected. This material induced mild scaling of the epidermis. Treatment-related skin tumors were not observed.
- (10) The commercial materials were characterized by gas and liquid chromatography, spectrometry, potentiometric titration, and vapor pressure as osmometry. The findings are summarized in Appendix A.

- (11) Statistical methods have been developed that permit quantitation of skin tumorigenicity. Background information on the special statistical methods used is presented in Appendix C.

## INTRODUCTION

Epoxy resins are a diverse class of chemicals that differ in structure, physical properties, and, presumably, biological activity. The purpose of these experiments was to compare the chronic dermal toxicity and carcinogenicity of selected commercial epoxy resins and to determine the potential for positive synergistic carcinogenic interactions between different resins.

This work is an extension and continuation of a Department of Energy sponsored program to evaluate epoxy resins for potential occupational health risks. The materials examined were chosen on the basis of their interest to the U.S. government. They are representative of the manufacturer's production at the time, and therefore the data are completely valid only for the specific production period.

Results of the experimental exposures will be reported in two parts. This report describes the test materials, their chemical and physical characteristics and the experimental design. General (systemic) toxicity will be evaluated and the skin carcinogenicity of the materials compared. A subsequent report will provide morphological descriptions of skin and significant internal pathology induced by the various treatments.

## MATERIALS AND METHODS

## Test Materials

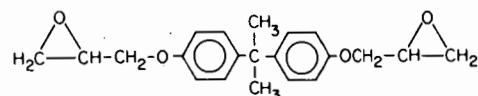
Figure 1 provides the structure, systematic name and Chemical Abstracts (CAS) registry number for the main component of five named epoxy resins (I-VII), two amine curing agents (VIII, IX), and B(a)P (X) which was used as a standard reference skin carcinogen. The commercial sources of the materials are given in Table 1. It is important to realize that the test materials are commercial/proprietary products rather than individual chemical compounds. Thus, materials I, II, and III are similar insofar as

Table 1. Source, identity and purity of test materials

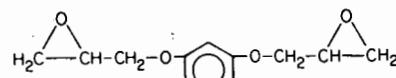
Material	Manufacturer	Trade name	Batch No.	Purity (wt %)
I	Celanese Coatings	Epi-Rez 508	MC8684	97
II	Shell Chemical	Epon 828	8WHJ17	89
III	Ciba Geigy	Araldite 6010	BAP-427	87
IV	Ciba Geigy	ERE 1359	P6602	88
V	Ciba Geigy	XB 2793	BAR90786	89
VI	Wilmington Chemical	HeLoxy WC68	GGG1367	70
VII	Union Carbide	ERR 4205	-	97
VIII	Applied Plastics	Apco 2330	J7-017	93
IX	Rohm and Haas	Menthane diamine	G5783	85
X	Aldrich Chemical	Benzo( <u>a</u> )pyrene	031777	99

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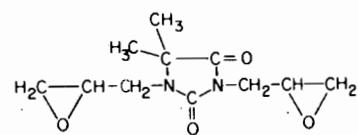
I, II, III 2,2'-(1-methylethyldene) bis(4,1-phenyleneoxymethylene) bisOxirane 1675-54-3



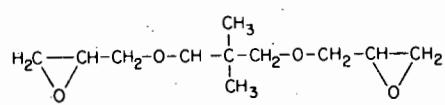
IV 2,2'-[1,3 phenylenebis (oxymethylene)]bisOxirane 101-90-6



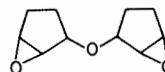
V 5,5-Dimethyl-1,3-bis (oxiranylmethyl)-2,4-Imidazolidinedione 15336-81-9



VI 2,2'-(2,2-dimethyl-1,3-propanediyl) bis (oxymethylene) bisOxirane 17557-23-2



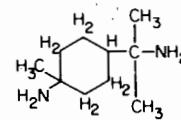
VII Bis(2,3-epoxycyclopentyl) ether 2386-90-5



VIII 1,3-Benzenediamine 108-45-2



IX 4-amino- $\alpha,\alpha,4$ -trimethylcyclohexanemethamine 80-52-4



X Benzo[ $\alpha$ ]pyrene 50-32-8

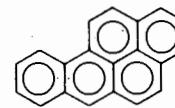


Fig. 1. Structures for the named principal component of commercial epoxy resins and amine curing agents. A roman numeral identifier, systematic name, and Chemical Abstracts registry number is given above each structure.

their main component is DGEBA (see Fig. 1) and oligomers derived from it. However, they also contain small quantities of impurities. Further details concerning the chemical characterization of these materials can be found in Appendix A. In Table 1, purity refers to the amount, by weight, of the named chemical (plus oligomers for I, II, and III) in the commercial product.

All the materials in Table 1, with the exception of VII, were applied separately. Material VII had been tested previously (1,2) and therefore was not retested singly; in the current study it was tested in an equal parts (by volume) mixture with materials I, II, and III. Materials V and VI were also tested in combination but at 70:30 (by volume). Letter codes are used in the text and tables to identify each mixture: (A) 50:50 mixture of III and VII; (B) 70:30 mixture of V and VI; (C) 50:50 mixture of I and VII; and (D) 50:50 mixture of II and VII.

#### Animal Exposures

Inbred, male and female C3Hf/Bd mice were produced under pathogen-free barrier conditions and held under these conditions for the 24-month duration of the experiment. Mice were weaned at 3-4 weeks of age. At 10 weeks of age the hair was removed from the back with electric clippers and the animals were randomly assigned in groups of five to each treatment dose combination. Mice were housed in polycarbonate shoebox cages with hardwood chip bedding. Food (Purina 5010-C) and water were constantly available.

The dose levels for each material were selected on the basis of a 2-week, five times weekly application of the test materials dissolved in spectro-grade acetone (Matheson-Coleman-Bell). The highest dose for the

2-year exposure was one which could be tolerated without irreversible local skin toxicity or systemic toxicity as reflected by suppression of weight gain or mortality. In some instances (materials I-III), when no significant local or systemic toxicity was observed, the viscosity of the material determined the concentration which could be reproducibly applied to the animals. The concentrations, number of mice per sex, and dose are given in Table 2. For mixtures A-D, the highest dose was set equal to the most toxic component. B(a)P (X) was diluted so that the level of response and distribution of times to skin tumor appearance would be similar to that of a weak skin carcinogen.

At the start of the experiment all materials, except IX and X, were weighed into glass scintillation vials in an amount sufficient to yield the highest concentration after the addition of an appropriate volume of acetone. The vials were kept in the dark at 4°C until used. Because material IX was so unstable that it could not be distributed, it was kept in a dessicator under nitrogen and weighed into vials immediately before solvent dilution. Material X was made from a concentrated stock solution kept at room temperature in a foil-wrapped container.

The material was applied with a 50- $\mu$ l micropipette on Monday, Wednesday, and Friday, excluding holidays. Mice were reshaved as required. The time of neoplasm appearance was taken as the day on which a raised, circumscribed lesion appeared in the treated area of skin that persisted for the duration of the experiment or until death. The time of initial appearance as the basis for comparison of different materials is preferred to other indices, such as time to reach some arbitrary diameter, because tumor volumes can vary

greatly as a consequence of secondary infection, amount and accumulation of keratin produced, and growth behavior of individual neoplasms.

Table 2. Experimental design

Material	No. of mice		Material concentration (wt/vol %)	Dose (mg/week) <sup>a</sup>
	Female	Male		
I	40	40	50	75
II	40	40	50	75
III	40	40	50	75
IV	25	25	1.25,0.63,0.32	1.8,0.9,0.45
V	25	25	2.5,1.25,0.63	3.75,1.87,0.94
VI	25	25	2.5,1.25,0.63	3.75,1.87,0.94
VII <sup>b</sup>	40	40	50,10	75,15
VIII	25	25	6,3,1.5	9,4.5,2.25
IX	25	25	2,1,0.5	3,1.5,0.75
X	50	50	0.01,0.005,0.0025, 0.00125	0.015,0.0075,0.00375, 0.001875
A	25	25	50,25,12.5	75,37.5,18.75
B	25	25	2.5,1.25,0.63	3.75,1.87,0.94
C	25	25	50,25,12.5	75,37.5,18.75
D	25	25	50,25,12.5	75,37.5,18.75
Acetone	150	150	100	150

<sup>a</sup>Unit density assumed for all materials.

<sup>b</sup>Data obtained previously and included for comparison with the current materials.

#### Parameters of Chronic Dermal Toxicity

At intervals throughout the experiment body weight was determined, by cage group, at the highest concentration of each material. Cumulative mortality was noted. Heparinized blood samples taken from a random sample of mice surviving the full 24-month exposure were submitted to the clinical laboratory of the ORNL Health Division. For each sample total red and white cell counts, hematocrit, and hemoglobin were determined before the sample was centrifuged to recover the plasma. The plasma was subjected to analysis for total protein, albumin, glutamic-oxalacetic transaminase, alkaline phosphatase, urea nitrogen, glucose and triglycerides. Procedures used and other methodological details can be found in Appendix B. Time to skin tumor observation was, as previously noted, the primary criterion used for comparison of different material-dose groups. The viscera were examined in animals that either died or were killed at the end of the study. Lesions noted were recorded on a standard form for each animal, and tissues were taken for histology only when the gross diagnosis was questionable.

#### Statistical Analysis

Body weight was evaluated by the t-test for comparison of treated group means with those of the vehicle control. Group means and standard errors were calculated for clinical hematologic and chemical parameters. The effect of treatment on systemic mortality and the effect of the presence of skin tumor on mortality were evaluated by means of the Mantel-Haenszel test on the force of mortality. The "force of mortality" for an animal alive at the beginning of a small time interval is the

probability of death in the interval divided by the length of the interval. Here each interval is taken to be 1 day. The degree of skin carcinogenicity was determined from parameters of the Weibull distribution fitted to the times to tumor for each animal. Potencies relative to material X were obtained for each of the test materials shown to elicit skin neoplasms. Details concerning the statistical theory and methods used can be found in Appendix C.

## RESULTS

## Acute Toxicity

Mortality was induced after daily dermal application of materials V, VIII, and IX for 2 weeks at concentrations of 20, 12, and 50%, respectively. None of the remaining materials was lethal. Maximum tolerated exposure was limited more by skin inflammation and necrosis than by acute lethality. Acute necrosis with sloughing was observed after one or two applications of materials IV, V, VI, and IX at concentrations greater than 10%. This irritant effect was also noted at lower concentrations, but with lesser degrees of cytotoxicity. Eventually a concentration was reached that could be tolerated without skin ulceration. Materials I, II, III, and VII, after a transient inflammatory response, were tolerated at the maximum concentrations permitted by viscosity. Material VIII was not a primary skin irritant but was systemically toxic. The observed acute toxic potential of these materials is summarized in Table 3. B(a)P (X) and acetone did not cause

Table 3. Concentration at which acute toxic effects were noted when epoxy resins and amine curing agents were applied to the intact skin

Material	Concentration at which effect was noted		
	Body weight loss	Mortality	Skin irritation
I, II, III, VII	none at 50%	none at 50%	mild and transient at 50%
IV	10%	none at 50%	severe above 1.25%
V	20%	20%	severe above 2.5%
VI	none at 50%	none at 50%	severe above 2.5%
VIII	12%	12%	none at tolerated levels
IX	10%	50%	severe above 2%

acute skin irritation, weight loss, or mortality at the concentration and volume applied. Mixtures A-D induced acute toxicity in proportion to the additive effect of each component.

#### Chronic Toxicity

Evaluation of chronic toxicity was based upon changes in body weight at the highest dose of each material, changes in force of non-skin tumor mortality and blood hematologic and chemical alterations at the highest dose level of each material, relative to the vehicle control.

#### Body Weight

Average body weights at different times during the experiment are given in Table 4. Body weight was significantly ( $P < 0.001$ ) suppressed at 24 months in male and female mice exposed to materials IV and VII. In all other groups average weight did not differ significantly ( $P > 0.05$ ) from that of the vehicle control.

#### Mortality

As a summary measure of overall mortality, we used 750-day survival (percent) as shown in Table 5A for female and 5B for male mice. Animals that were killed before 750 days were ignored in this calculation. Except for a few groups, which are indicated in the table, there were at most two such animals in each group.

Table 4. Body weight in male and female C3H mice exposed dermally at the highest dosage

Material	Sex	Average body weight (g ± SE) at		
		6 months	12 months	24 months
I	F	26.7 (0.8)	26.7 (0.6)	26.9 (0.9)
	M	34.2 (0.5)	33.4 (0.5)	31.8 (0.8)
II	F	27.9 (0.5)	27.5 (0.4)	27.7 (0.7)
	M	32.5 (0.2)	31.8 (0.3)	30.9 (0.4)
III	F	28.2 (0.5)	27.8 (0.6)	27.6 (0.4)
	M	32.8 (0.2)	31.8 (0.3)	30.6 (0.7)
IV	F	25.9 (0.3)	25.5 (0.2)	18 (1) <sup>a</sup>
	M	31.3 (0.5)	30 (0.3)	22 (0.7) <sup>a</sup>
V	F	26.6 (0.3)	26.4 (0.6)	26.2 (0.9)
	M	31.8 (0.6)	30.9 (0.4)	29.5 (0.6)
VI	F	27.6 (0.4)	27.4 (0.5)	27.5 (0.5)
	M	32.2 (0.6)	31.6 (0.7)	30.7 (0.4)
VII	F	n.d. <sup>b</sup>	n.d.	21.3 (0.7) <sup>a</sup>
	M	n.d.	n.d.	23.8 (0.8) <sup>a</sup>
VIII	F	27.1 (0.5)	26.3 (0.2)	25.7 (1.3)
	M	32.2 (1)	30.9 (1.1)	28.6 (0.5)
IX	F	29.2 (0.6)	27.8 (0.4)	28.3 (0.4)
	M	34.4 (1.2)	32.6 (1.1)	30.3 (1.2)
X	F	27.2 (0.4)	n.d.	n.d.
	M	32.3 (0.8)	n.d.	n.d.
A	F	27.2 (0.4)	27 (0.5)	26.8 (0.5)
	M	30.8 (0.2)	30.6 (0.4)	28.6 (0.4)
B	F	28.8 (0.8)	27.9 (0.8)	26 (0.8)
	M	32.8 (1)	32.9 (0.6)	30 (0.3)
C	F	27.2 (0.5)	27 (0.4)	26.5 (0.9)
	M	31.1 (0.4)	30.5 (0.3)	29.7 (0.6)
D	F	26.8 (0.4)	26.6 (0.5)	27.5 (0.5)
	M	30.6 (0.4)	30 (0.5)	30.2 (0.5)
Acetone	F	28.2 (0.5)	27.2 (0.3)	27.4 (0.3)
	M	33.4 (0.5)	31.8 (0.5)	30 (0.6)

<sup>a</sup>Mean body weight significantly different from that of vehicle control;  
 $P < 0.001$ .

<sup>b</sup>n.d. = not done.

Mortality differences can occur as a result of either systemic toxicity or skin tumors. To investigate systemic toxicity, we compared the force of non-skin tumor mortality in each treated group with that in the acetone controls. A summary chi-squared statistic based on the log-rank test (3) was computed in each case and is presented in Table 5A and B for females and males respectively. The validity of this test depends on the assumption that skin tumor incidence does not select either for or against animals that would otherwise have died later of another cause. In the absence of data on the cause of death, this assumption is not statistically testable. Significant ( $P < 0.05$ ) systemic mortality was noted at the higher doses, especially in female mice. Positive evidence of accelerated mortality in some, but not all treated groups indicates that the doses selected on the basis of a 2-week acute test do not accurately predict systemic toxicity.

Skin tumor-related mortality was assessed within each group by comparing the effect of presence of tumor on force of mortality. Statistical evidence ( $P < 0.05$ ) of skin-tumor related mortality was found for the B(a)P groups at dose = 0.0075 (males and females) and for the B(a)P treated females at dose = 0.0037. At the highest B(a)P dose (0.015) early sacrifice after tumor induction precluded assessment of tumor related mortality. The only other group to show skin-tumor related mortality was the high dose female group treated with material A. In many of the remaining groups, there were not enough animals at risk for natural death in the tumor-bearing and tumor-free states to permit a reasonably powerful statistical test. Lack of statistical significance should therefore not be interpreted as evidence that skin tumors had no effect on mortality.

Table 5. Overall and systemic mortality in C3H mice

Material	Dose	% Survival at 750 days (95% confidence limits)	$\chi^2$ for systemic mortality <sup>a</sup>
<u>A. FEMALES</u>			
I	75	58 (41-74)	12.95***
II	75	70 (55-85)	10.21**
III	75	65 (49-81)	13.10***
IV	1.8	17 (6-36)	66.61***
	0.9	64 (43-81)	3.93*
	0.45	84 (66-94)	0.22
V	3.75	24 (13-51)	8.55**
	1.87	60 (38-78)	2.11
	0.94	72 (53-88)	2.91
VI	3.75	80 (62-92)	0.54
	1.87	56 (34-76)	16.35***
	0.94	72 (53-88)	2.33
VII	75	51 (34-68)	4.95*
	15	62 (45-78)	1.53
VIII	9	44 (24-66)	28.07***
	4.5	68 (47-84)	1.37
	2.25	80 (62-92)	0.36
IX	3	84 (66-94)	0.00
	1.5	72 (53-88)	0.71
	0.75	64 (43-81)	0.83
X	0.015	<sup>b</sup> <u>-b</u>	0.65
	0.0075		0.46
	0.0037	68 (54-82)	0.20
	0.0019	66 (52-80)	4.95*

(Table 5 continued)

Table 5 (continued)

Material	Dose	% Survival at 750 days (95% confidence limits)	$\chi^2$ for systemic mortality <sup>a</sup>
A	75	80 (62-92)	0.07
	37.5	76 (57-89)	0.30
	18.75	72 (53-88)	1.30
B	3.75	68 (47-84)	1.38
	1.87	72 (53-88)	5.03*
	0.94	72 (53-88)	1.25
C	75	60 (38-78)	3.79
	37.5	56 (34-76)	3.66
	18.75	72 (53-88)	0.76
D	75	84 (66-94)	0.11
	37.5	68 (47-84)	2.62
	18.75	64 (43-81)	3.99*
Acetone	-	82 (76-88)	-
<u>B. MALES</u>			
I	75	83 (69-96)	1.07
II	75	85 (73-97)	0.27
III	75	79 (66-93)	0.83
IV	1.8	72 (44-88)	1.47
	0.9	72 (53-88)	0.76
	0.45	84 (66-94)	0.18
V	3.75	76 (57-89)	0.36
	1.87	84 (66-94)	0.13
	0.94	60 (38-78)	1.30
VI	3.75	88 (70-97)	0.76
	1.87	84 (66-94)	0.27
	0.94	80 (62-92)	0.07
VII	75	75 (60-90)	0.01
	15	68 (52-83)	0.19

(Table 5 continued)

Table 5 (continued)

Material	Dose	% Survival at 750 days (95% confidence limits)	$\chi^2$ for systemic mortality <sup>a</sup>
VIII	9	64 (43-81)	12.74***
	4.5	84 (66-94)	0.07
	2.25	80 (62-92)	0.23
IX	3	84 (66-94)	1.21
	1.5	80 (62-92)	0.02
	0.75	84 (66-94)	0.42
X	0.015	b	0.24
	0.0075	-b	1.57
	0.0037	82 (70-95)	0.00
	0.0019	82 (70-94)	0.03
A	75	72 (53-88)	1.96
	37.5	80 (62-92)	0.17
	18.75	68 (47-84)	4.48*
B	3.75	54 (34-75)	0.05
	1.87	84 (66-94)	0.21
	0.94	76 (57-89)	0.00
C	75	71 (50-88)	0.01
	37.5	92 (76-99)	1.37
	18.75	80 (62-92)	0.03
D	75	92 (75-98)	1.93
	37.5	76 (57-89)	1.06
	18.75	92 (76-99)	2.20
Acetone	-	83 (77-90)	-

<sup>a</sup>\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

<sup>b</sup>B(a)P groups sacrificed after 100% tumor response, before 750 days.

### Clinical Hematologic Evaluation

Toxic suppression of bone marrow and lymphatic tissues was evaluated by examining the cellular composition of peripheral blood in a randomly selected subset of animals which survived to the end of the experiment. Blood was collected by cardiac puncture, under Metofane® (Pitman-Moore) anesthesia, into a syringe which contained heparin to prevent coagulation. The samples were evaluated for total red cell count, total white cell count, hemoglobin, and hematocrit by use of conventional clinical laboratory procedures (refer to Appendix B for details). Treatment-related effects were evaluated by comparison of the data with that from acetone controls, while age- (or acetone-) related changes were evaluated by comparison of vehicle control with 10- to 12-week-old untreated mice (aging control). Only the highest dose of each material was evaluated, with the exception of material IV, for which body weight suppression and mortality provided evidence of systemic toxicity. Hematologic data are presented in Table 6.

The data indicate an age- (or acetone-) related decrease in the number of circulating red cells and a proportionate decrease in hemoglobin and hematocrit in all treated animals. White cell counts fluctuated widely, with leukocytosis noted in groups in which skin tumors were induced (V, VI, X, B, C, D). Higher-than-normal white blood cell counts in these groups most probably are due to inflammation following necrosis and infection of skin neoplasms. Leukopenia was noted with material IV at the two highest dose levels. Because differential counts were not done, it is not possible to determine whether suppression of lymphocytes, granulocytes, or both, contributed to the decrease in white cell numbers. The fact that red cell

Table 6. Blood counts in C3H mice exposed dermally for 24 months to epoxy resins and amine curing agents

Material	Dose (mg/week)	Sex	No. of animals	Average values (SE)			
				Red cell ( $\times 10^{-6}/\text{mm}^3$ )	White cell ( $\times 10^{-3}/\text{mm}^3$ )	Hematocrit (%)	Hemoglobin (g/100 ml)
I	75	F	5	7.14 (0.21)	5.74 (0.66)	36.4 (1.2)	13.1 (0.29)
	75	M	5	6.59 (0.84)	7.22 (0.48)	33.6 (0.51)	11.6 (0.28)
II	75	F	5	6.32 (0.28)	6.9 (1.0)	32.4 (1.4)	11.5 (0.62)
	75	M	5	6.64 (0.17)	8.12 (2.55)	32.8 (0.73)	11.7 (0.31)
III	75	F	5	6.51 (0.57)	7.44 (1.25)	34.4 (0.4)	12.1 (0.17)
	75	M	5	6.78 (0.23)	9.88 (1.87)	34.0 (1.4)	12.0 (0.41)
IV	1.8	F	2	no sample			
	1.8	M	13	7.66 (0.19)	4.38 (0.41)	35.0 (0.59)	13.3 (0.33)
	0.9	F	5	6.68 (0.20)	4.14 (0.68)	33.2 (1.25)	12.0 (0.36)
	0.9	M	5	6.26 (0.50)	4.66 (0.50)	32.8 (1.46)	11.3 (0.84)
	0.45	F	5	6.14 (0.25)	5.88 (1.55)	32.0 (0.94)	11.88 (0.44)
	0.45	M	5	6.99 (0.17)	6.5 (0.50)	34.6 (0.75)	12.7 (0.29)
V	3.75	F	5	5.54 (0.39)	8.4 (4.07)	31.4 (2.06)	10.56 (0.75)
	3.75	M	5	6.05 (0.45)	15.4 (5.12)	34.6 (0.6)	12.14 (0.46)
VI	3.75	F	5	5.84 (0.36)	6.22 (1.37)	33.0 (1.64)	11.5 (0.49)
	3.75	M	5	6.34 (0.36)	13.48 (6.4)	32.0 (1.67)	11.2 (0.73)
VIII	6	F	5	6.54 (0.07)	6.16 (0.89)	35.0 (1.05)	11.9 (0.26)
	6	M	5	7.14 (0.16)	7.94 (0.34)	35.8 (1.56)	12.8 (0.37)
IX	3	F	5	6.38 (0.15)	6.88 (1.01)	32.4 (1.12)	11.6 (0.38)
	3	M	5	7.70 (0.68)	7.50 (1.18)	37.6 (3.37)	13.2 (1.08)
X	0.00375	F	10	5.96 (0.19)	13.32 (6.4)	29.65 (0.84)	10.86 (0.43)
	0.00375	M	10	6.22 (0.33)	12.08 (5.0)	31.5 (1.48)	11.34 (0.57)
A	75	F	5	6.24 (0.26)	5.7 (0.97)	33.0 (0.55)	11.5 (0.38)
	75	M	5	6.82 (0.53)	7.8 (1.17)	35.8 (3.64)	12.5 (1.16)
B	3.75	F	5	5.34 (0.47)	10.5 (3.35)	30.6 (2.58)	10.48 (0.93)
	3.75	M	5	5.06 (0.32)	21.4 (4.91)	32.8 (1.68)	10.08 (0.44)
C	75	F	5	6.44 (0.20)	6.06 (1.53)	35.0 (1.0)	11.96 (0.35)
	75	M	5	6.43 (0.14)	13.64 (8.92)	33.2 (0.49)	11.56 (0.16)
D	75	F	5	5.69 (0.48)	8.5 (1.96)	29.0 (1.52)	10.04 (0.54)
	75	M	5	5.96 (0.36)	14.3 (5.23)	30.2 (1.2)	10.6 (0.57)
<b>Acetone</b>							
control	--	F	20	6.14 (0.18)	5.3 (0.66)	31.65 (0.51)	11.11 (0.32)
		M	20	6.39 (0.26)	7.02 (0.88)	32.15 (0.89)	11.58 (0.49)
<b>Aging</b>							
control	--	F	10	7.18 (0.07)	4.44 (0.51)	38.0 (0.39)	13.63 (0.11)
		M	10	7.44 (0.07)	5.58 (0.24)	39.9 (0.28)	13.06 (0.11)

numbers were not reduced in animals exposed to material IV makes it least likely that bone marrow toxicity caused the leukopenia. By default, it is more likely that toxicity to lymphatic tissues reduced the cell count. Hematologic data are not available for material VII by itself. However, to the extent that its effects would be observed as a component in the A, B, C, and D mixtures, there appears to be no significant effect of this material on circulating cells.

#### Clinical Chemical Evaluation

In conjunction with the determination of the cellular composition of blood, the plasma from the same animals was also subjected to a battery of routine assays to detect systemic or organ-specific toxicity. The results of these determinations are summarized in Table 7. The methods and procedures used are described in Appendix B.

Plasma total protein levels were increased as a function of age in both sexes, with occasional high average levels noted in males. Alkaline phosphatase levels varied widely, both within and between groups. It appeared that female C3H mice had significantly higher alkaline phosphatase levels than males, irrespective of age. Glutamic-oxalacetic transaminase levels were relatively uniform across groups and between sexes, but the range of standard errors gives a clear indication of underlying individual heterogeneity. Glucose levels were little affected by sex or age. A clear treatment- and dose-related hypoglycemia was noted in both male and female mice exposed to material IV. Triglyceride levels varied widely, with no clear indication of an effect of treatment or age, although levels were

Table 7. Clinical chemical evaluation of C3H mice exposed dermally for 24 months to epoxy resins and amine curing agents<sup>a</sup>

Material	Dose (mg/week)	Sex	No. of animals	Total protein (g/dl)	Alkaline phosphatase (units/liter at 30°C)	Glutamic- oxalacetic transaminase (units/liter at 30°C)	Glucose (mg/dl)	Triglycerides (mg/dl)	Urea nitrogen (mg/dl)
I	75	F	5	5.0 (0.1)	70 (8)	52 (4)	94 (12)	127 (25)	35 (2)
	75	M	5	5.1 (0.2)	60 (3)	51 (11)	79 (11)	88 (11)	33 (2)
II	75	F	5	5.2 (0.3)	109 (24)	51 (8)	72 (8)	97 (17)	38 (2)
	75	M	5	5.4 (0.1)	53 (4)	31 (1)	104 (6)	128 (20)	27 (1)
III	75	F	5	4.9 (0.1)	135 (25)	82 (37)	96 (6)	92 (17)	30 (2)
	75	M	5	5.3 (0.3)	52 (8)	82 (45)	85 (8)	134 (20)	41 (3)
IV	1.8	F	2	4.8 (0.03)	74 (3)	55 (6)	44 (10)	77 (15)	30 (2)
	1.8	M	13	5.0 (0.1)	62 (3)	71 (6)	55 (5)	79 (10)	35 (2)
	0.9	F	5	5.1 (0.4)	129 (30)	93 (35)	50 (11)	112 (36)	40 (9)
	0.9	M	5	5.2 (0.2)	63 (3)	56 (6)	64 (8)	88 (15)	29 (2)
	0.45	F	5	5.2 (0.1)	126 (17)	40 (2)	98 (10)	94 (14)	27 (2)
	0.45	M	5	5.4 (0.1)	71 (11)	47 (7)	97 (5)	238 (23)	46 (1)
V	3.75	F	5	n.d.	188 (69)	n.d.	80 (6)	75 (7)	34 (3)
	3.75	M	5	5.3 (0.05)	60 (5)	49 (6)	76 (13)	149 (33)	41 (2)
VI	3.75	F	5	5.2 (0.2)	167 (69)	49 (4)	96 (3)	188 (18)	35 (4)
	3.75	M	5	5.7 (0.2)	99 (39)	39 (7)	81 (7)	167 (39)	43 (7)
VIII	6	F	5	n.d.	109 (12)	n.d.	95 (5)	100 (13)	29 (2)
	6	M	5	5.2 (0.2)	55 (2)	48 (6)	107 (6)	115 (24)	38 (4)
IX	3	F	5	5.5 (0.1)	106 (15)	62 (11)	115 (5)	139 (30)	37 (4)
	3	M	5	6.5 (0.2)	100 (31)	79 (15)	107 (16)	151 (23)	45 (2)

(Table 7 continued)

Table 7 (continued)

Material	Dose (mg/week)	Sex	No. of animals	Total protein (g/dl)	Alkaline phosphatase (units/liter at 30°C)	Glutamic- oxalacetic transaminase (units/liter at 30°C)	Glucose (mg/dl)	Triglycerides (mg/dl)	Urea nitrogen (mg/dl)
X	0.00375	F	10	5 (0.5)	103 (19)	70 (26)	82 (11)	96 (27)	34 (3)
	0.00375	M	10	5 (0.1)	59 (6)	46 (5)	92 (6)	118 (32)	35 (2)
A	75	F	5	5.6 (0.2)	73 (10)	41 (2)	104 (7)	128 (20)	31 (3)
	75	M	5	5.3 (0.1)	52 (3)	40 (4)	85 (13)	194 (34)	45 (2)
B	3.75	F	5	5.2 (0.07)	97 (12)	97 (46)	82 (8)	95 (25)	40 (4)
	3.75	M	5	5.4 (0.1)	55 (8)	51 (11)	90 (11)	165 (35)	42 (5)
C	75	F	5	5.5 (0.3)	83 (20)	41 (3)	112 (5)	98 (15)	26 (1)
	75	M	5	5.8 (0.1)	51 (3)	44 (8)	100 (13)	103 (12)	27 (1)
D	75	F	5	5.3 (0.2)	84 (18)	44 (9)	111 (12)	77 (16)	40 (8)
	75	M	5	6.4 (0.3)	39 (4)	60 (6)	120 (6)	123 (12)	38 (1)
Acetone control	-	F	20	5.4 (0.1)	148 (34)	70 (16)	88 (6)	95 (18)	32 (3)
	-	M	20	5.5 (0.3)	57 (9)	112 (28)	78 (9)	119 (25)	40 (4)
Aging control	-	F	10	4.9 (0.07)	74 (2)	58 (18)	112 (5)	126 (16)	24 (2)
	-	M	10	4.9 (0.06)	51 (2)	82 (22)	98 (4)	216 (14)	30 (1)

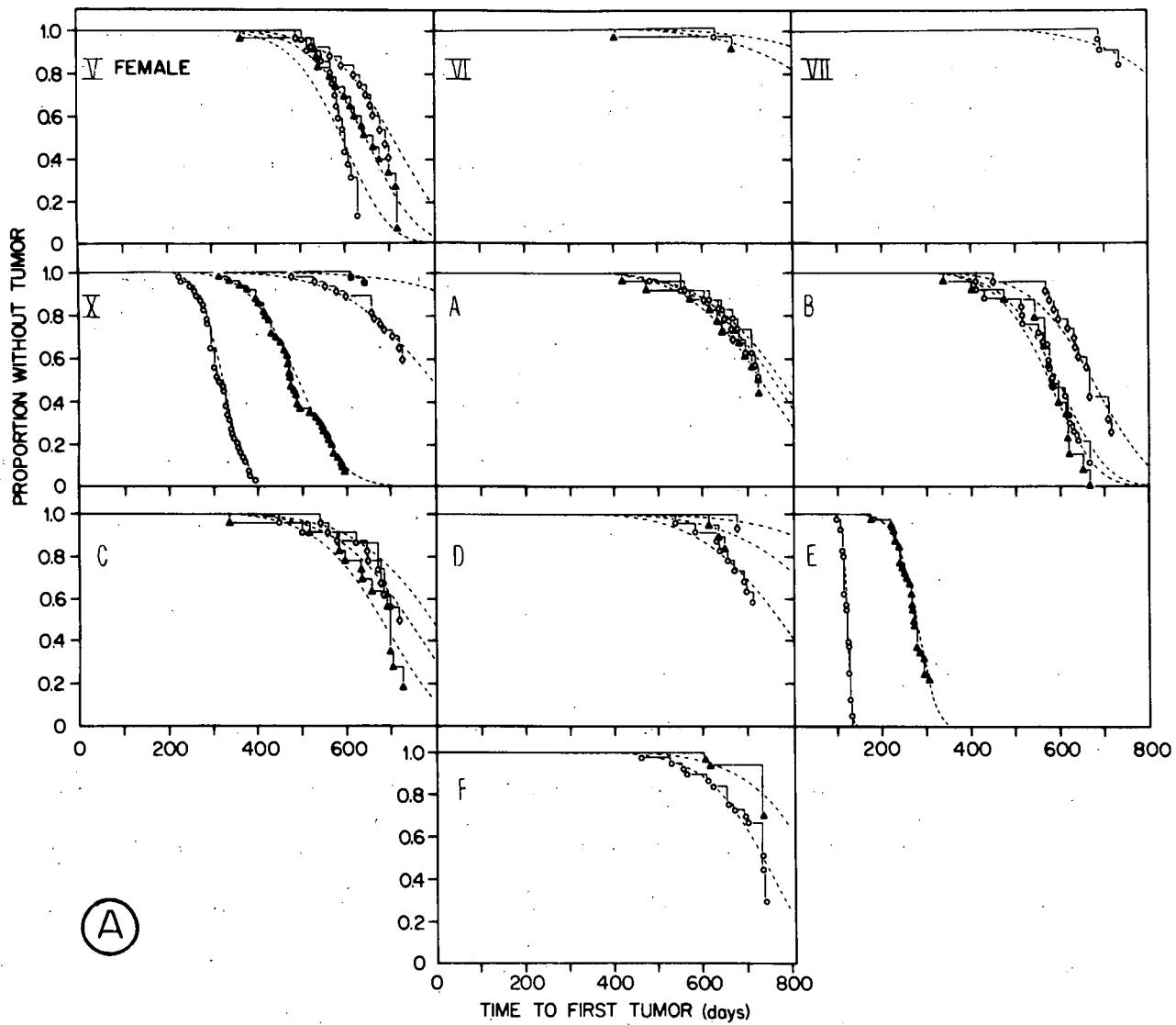
<sup>a</sup>Values given are mean (SE).

consistently higher in males than in females. Urea nitrogen levels were higher in males than females and also increased as a function of age. Treatment-related differences were not apparent, although standard errors again suggested considerable variation among individual animals.

Taken together, these data amplify and confirm the evidence that material IV is a systemic toxin at dose levels that fail to induce either skin irritation or neoplasia. Since clinical hematologic and chemical analyses were conducted on individual animals and each animal was also subjected to gross and microscopic evaluation, it eventually will be possible to correlate clinical findings with gross and microscopic pathologic changes. This information will be included in a subsequent report.

#### Skin Neoplastic Changes

Treatment-related skin neoplasms that were persistent, grew progressively, and contributed to mortality were induced with materials V, VI, VII, and X and with all the resin mixtures (A-D). For interpretation of the tumorigenic properties of each material, independent of natural or treatment-related mortality, the proportion of animals with skin tumors was corrected for deaths in animals before tumor occurrence by the Kaplan-Meier procedure (5). The resulting step curves, relating duration of exposure and probability of surviving without a skin neoplasm, are given in Fig. 2A and B for females and males, respectively. Differences between the distributions for males and females were tested by use of the log-rank test (3) and found to be significant ( $P < 0.05$ ) in many cases; therefore the results are presented separately for each sex.



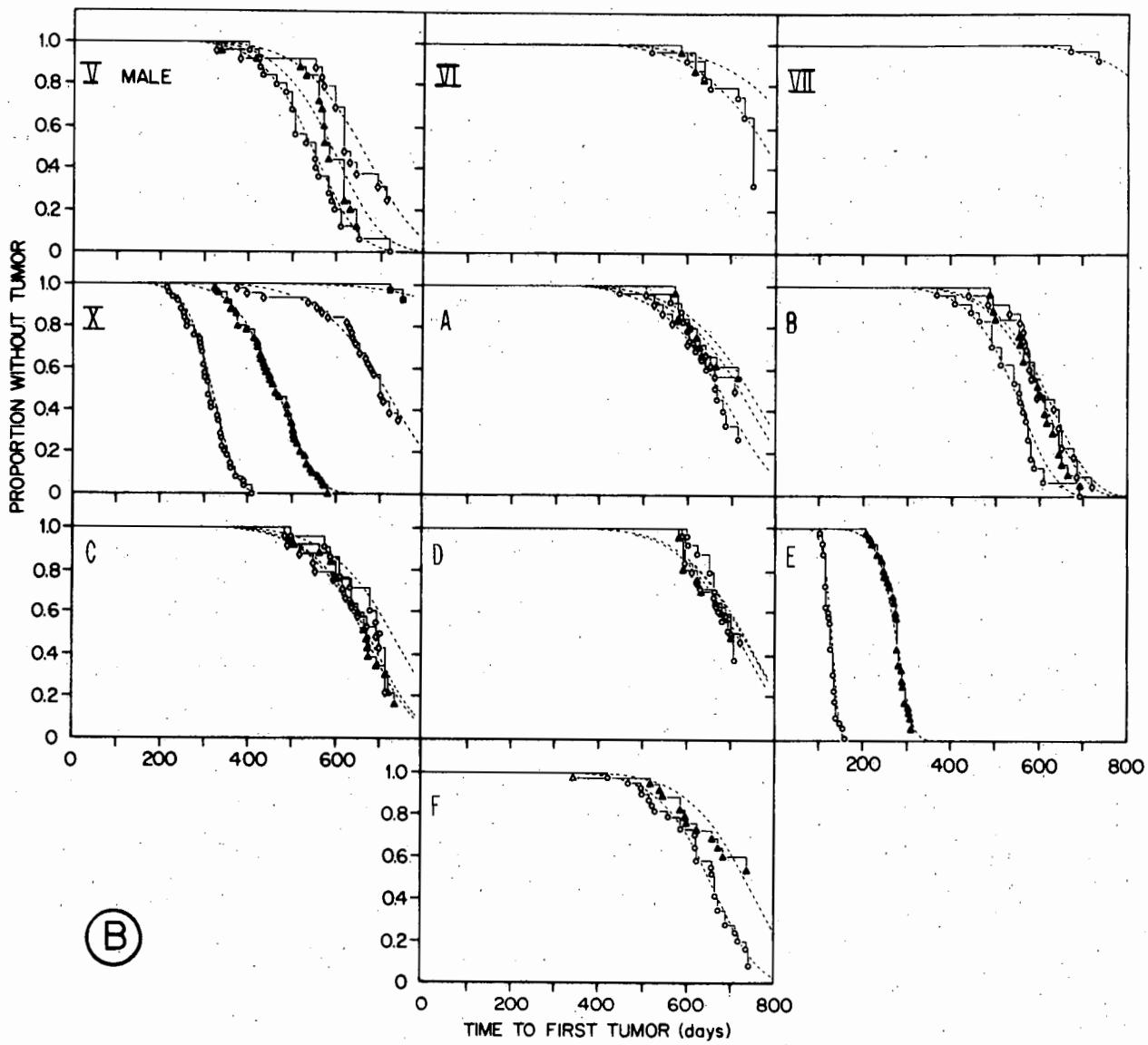


Fig. 2. Distribution of times to skin tumor for female (A) and male (B) C3H mice. Solid lines, Kaplan-Meier proportions; dashed lines, fitted Weibull. When dose responses are either absent or very shallow (Panels A-D) the lines cannot be distinguished. Each panel is identified with the material symbols used in the text. Panel E is the B(a)P control, and panel F the mixture of material VII and the Union Carbide DGEBA tested previously. The data in Panels E and F are included for comparison with the current materials. Symbols correspond to the dosages applied (mg/week) and, in order of decreasing dose, were  $\circ$ ,  $\blacktriangle$ ,  $\diamond$ ,  $\blacksquare$  for one or more dosages of each material shown to induce skin neoplasms under the prevailing test conditions.

The log-rank test was used again to test for dose-dependent differences among the distributions for each material-sex combination. Differences were not observed ( $P > 0.05$ ) for material VI in females, for material VII and mix D in males, or for mixes A and C in either sex. All other positive treatment groups demonstrated significant differences due to dose.

The Kaplan-Meier procedure is a useful means of displaying the distribution of times to tumor, requiring minimal assumptions. However, for quantification of the dose-response relationships, further assumptions need to be made. One usual assumption is that the distribution of time to tumor belongs to some parametric family of distributions. Past experiences (6-8) indicate that the Weibull distribution is frequently a good model in continuous skin carcinogenesis experiments. Accordingly, a restricted three-parameter Weibull distribution was fit for each treatment combination. (The restrictions on the Weibull fits concern assumptions needed for dose-response quantification. Details concerning the Weibull model and the fitting may be found in Appendix C.) The resulting Weibull fits are shown as dashed lines in Fig. 2, superimposed on the Kaplan-Meier step functions. As a summary and comparison measure, the expected median time to tumor response, (T50) was calculated from the fitted Weibull for each dose group eliciting at least one skin tumor, together with an approximate standard error (Table 8).

Comparison of different treatment groups on the basis of T50 reveals substantial differences among the materials. Males were more susceptible than females for all materials in which the response was adequate. Just as was observed in previous experiments, materials I, II, and III proved to be synergistic with material VII, on the basis of higher incidence and more

Table 8. Incidence and estimated time to median skin tumor response for materials in which one or more persistent skin tumors were observed

Material	Dose (mg/week)	Sex	No. at start	No. with tumor	T50 (SE) (days)
V	3.75	F	25	16	593 (19)
	3.75	M	25	24	542 (16)
	1.87	F	25	18	646 (20)
	1.87	M	25	22	587 (18)
	0.94	F	25	12	706 (27)
	0.94	M	25	15	654 (24)
VI	3.75	F	25	1	1183 (236)
	3.75	M	25	9	781 (38)
	1.87	F	25	2	991 (136)
	1.87	M	25	4	879 (67)
VII	75	F	40	3	922 (84)
	75	M	40	2	931 (82)
A	75	F	25	10	752 (37)
	75	M	25	15	671 (24)
	37.5	F	25	11	726 (33)
	37.5	M	25	10	738 (33)
	18.75	F	25	8	771 (43)
	18.75	M	25	10	716 (32)
B	3.75	F	25	20	592 (18)
	3.75	M	25	22	542 (15)
	1.87	F	25	20	573 (17)
	1.87	M	25	22	597 (17)
	0.94	F	25	18	671 (23)
	0.94	M	25	21	612 (18)
C	75	F	25	6	796 (50)
	75	M	25	10	729 (30)
	37.5	F	25	14	682 (26)
	37.5	M	25	20	664 (20)
	18.75	F	25	10	743 (35)
	18.75	M	25	17	672 (21)
D	75	F	25	9	776 (41)
	75	M	25	14	711 (24)
	37.5	F	25	3	912 (90)
	37.5	M	25	10	724 (30)
	18.75	F	25	1	1110 (197)
	18.75	M	25	13	727 (26)
X	0.015	F	45	44	322 (6)
	0.015	M	50	48	317 (7)
	0.0075	F	50	45	493 (12)
	0.0075	M	50	50	464 (10)
	0.0038	F	50	16	792 (35)
	0.0038	M	45	26	710 (20)
	0.0019	F	50	2	1164 (170)
	0.0019	M	50	2	1123 (139)

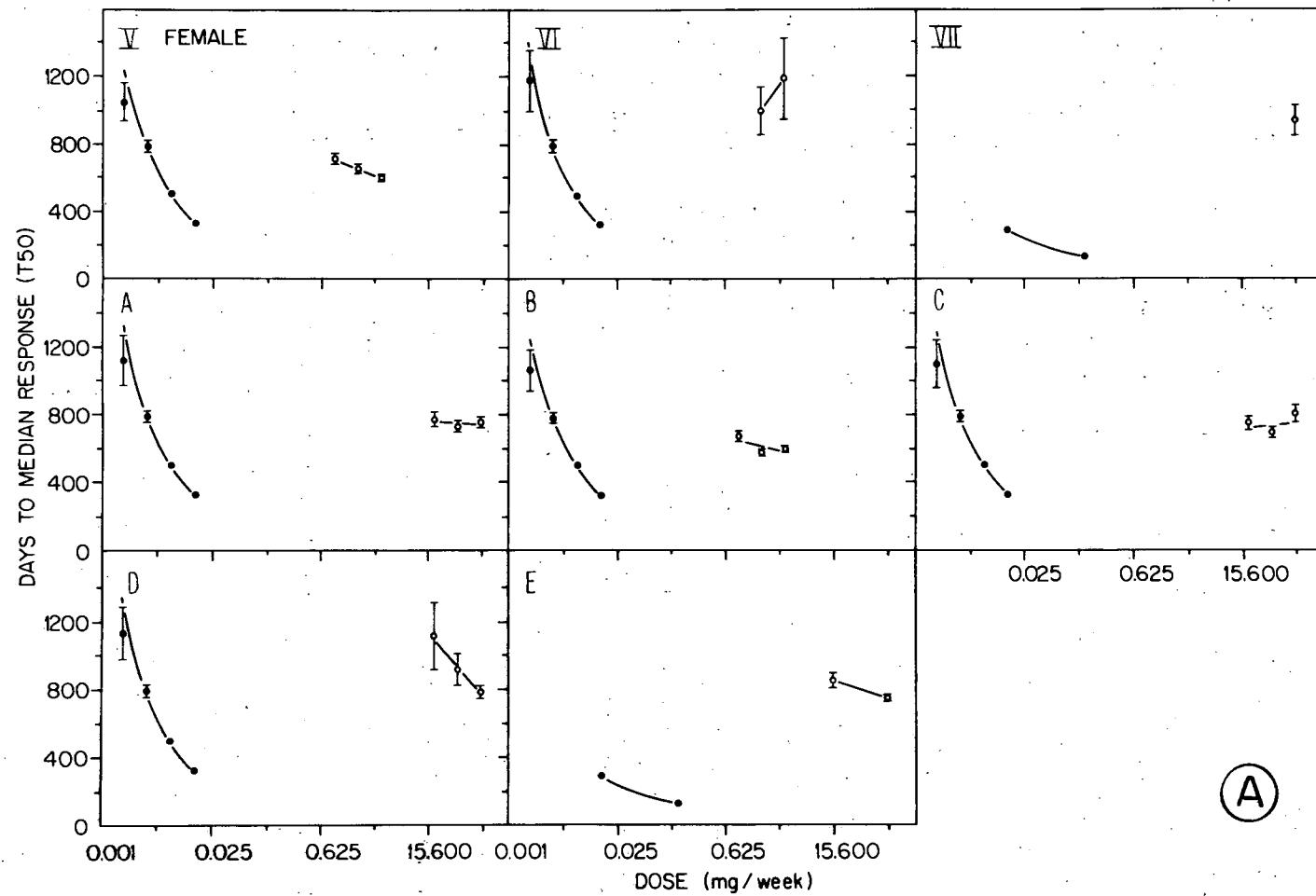
rapid rate of tumor occurrence observed for resin mixtures A, C, and D than observed for either component alone. Mixture B does not exhibit synergism but rather the additive effects of the individual components, i.e., the activity of the combined treatment does not exceed that of either component tested separately.

#### Determination of Carcinogenic Potency

For comparison of different treatments within a single experiment as well as experiments done at different times but in the same sex and strain, a potency index has been calculated for each treatment-dose combination relative to that obtained for the reference carcinogen (X). The potency index is the ratio of the dose of the reference carcinogen to that of the test material at an equivalent effect level. Here the "effect" was defined to be estimated median time to skin tumor, based upon a three-parameter Weibull fit to each material-dose combination with the shape ( $k$ ) and location ( $w$ ) parameters of the model held constant for all doses of the reference carcinogen and test material. In several cases there was evidence that the assumption of common  $k$  and  $w$  was not valid. However, an alternative computation of potency index in these cases had little effect on the conclusions. (See Appendix C for details concerning the potency calculations and the evaluation of the assumptions on which they were based).

In Fig. 3 the dose-effect observed for the reference carcinogen is compared with that obtained for each dose level of the unknown. Over the experimental dose range two features are apparent: (a) the effect changes more rapidly as a function of dose with the reference carcinogen (X) than

with any of the test materials; (b) for several materials, a change in effect with increasing dose is either very slight or absent. In view of these observations we have evaluated relative potency for each dose; values are given in Table 9 for each sex. Note that the systematic differences between sexes largely disappear when the potency is evaluated on a relative basis. Diminishing potency with increasing dose occurs because the median time to tumor for the reference carcinogen decreases much more rapidly with increasing log dose than does the median time to tumor for the test materials. An arbitrary, but perhaps valid, means of comparing the different materials would be to contrast the relative potencies at the highest exposure level permitted by local or systemic toxicity. By this convention the potencies of materials V and VI are an order of magnitude greater than those observed at the highest permissible doses of either material VII alone or material VII in combination with materials I, II, or III. Material VII exhibits positive synergistic interaction with materials I, II, and III (groups A, C, and D). The combination of materials V and VI (group B) induces a response comparable to that of material V, with no indication of synergism. By way of comparison the data shown in panel E is a previously tested Union Carbide DGEBA base resin together with the contemporary B(a)P reference standard. The response observed is comparable to that observed for the other combinations of DGEBA with material VII (groups A, C, and D).



(A)

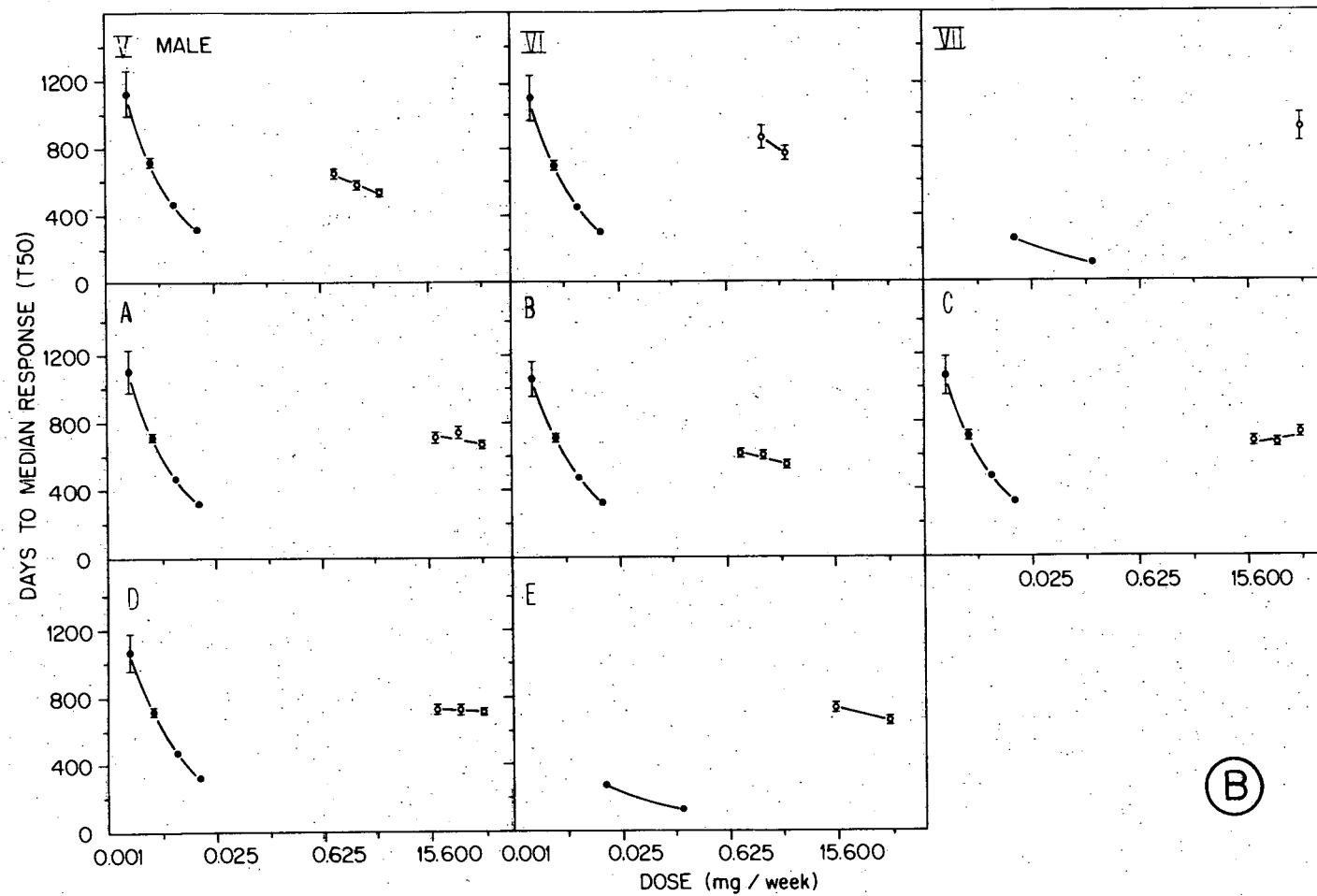


Fig. 3. Comparison of the dose effect obtained for B(a)P (●) with that of each unknown (○) for female (A) and male (B) C3H mice. The points on the ordinate are the maximum likelihood estimates of T50 and on the abscissa are dose on a logarithmic scale. One standard error is shown for each estimate of T50. The solid line connecting the points for each material is the weighted, least-squares best fit to the observed data. Panels are identified for each unknown compared with the concurrent B(a)P positive control. The data in Panels VII and E were obtained previously and are included for comparison with current materials.

Table 9. Skin carcinogenicity of B(a)P relative to that of epoxy resins and resin combinations

Material	Dose (mg/week)	Relative potency <sup>-1</sup> (lower 95% confidence limit)	
		Female	Male
V	0.94	218 (186)	218 (207)
	1.87	380 (341)	373 (360)
	3.75	667 (578)	640 (614)
VI	1.87	660 (386)	713 (617)
	3.75	1,640 (774)	1,180 (1,070)
VII <sup>a</sup>	75	55,400	206,000
A	18.75	4,740 (3,890)	5,300 (4,650)
	37.5	9,350 (8,140)	9,980 (9,100)
	75	18,400 (15,300)	18,800 (16,800)
B	0.94	190 (152)	200 (184)
	1.87	347 (297)	359 (337)
	3.75	638 (519)	647 (595)
C	18.75	4,380 (3,390)	4,470 (3,970)
	37.5	9,000 (7,450)	9,480 (8,640)
	75	18,500 (13,700)	20,100 (17,500)
D	18.75	7,730 (5,110)	5,280 (4,960)
	37.5	12,300 (9,840)	10,400 (9,890)
	75	19,600 (16,300)	20,300 (19,100)

<sup>a</sup>Data obtained previously and included for comparison with current materials; confidence limit not calculated due to insufficient dose-effect data.

## DISCUSSION

The present data demonstrate the chronic toxicity and skin carcinogenicity of selected commercial epoxy resin formulations applied as dilute acetone solution to the skin of C3H mice. An order of magnitude or greater difference in potency was noted. In general, male mice were more sensitive to skin tumor induction than female mice, whereas females were more sensitive to systemic toxicity. The potential for synergistic interaction between different materials was evaluated by application of resin mixtures. It had been noted previously (2) that material VII interacted synergistically with a Union Carbide product generically similar to I, II and III. Since this previously tested Carbide material was later found to contain appreciable amounts of epichlorohydrin and other nontypical components (see Appendix A), it was possible that synergism was due to these contaminants and not to the resin monomers as had been originally suspected. The present demonstration of an equivalent degree of synergism between VII and each of three separate resins obtained from different sources each with low but different levels of epichlorohydrin suggests strongly that synergism is between the principal components.

Skin neoplasms were not induced by materials I, II, III, IV, VIII, and IX at the dosage levels applied to C3H mice. Materials IV and IX are noteworthy in that both are corrosive on mouse skin and thus must be applied at low concentration. Material IV also attracts attention as a potential systemic toxicant at levels of exposure that do not induce local irritation. Additional long-term feeding studies to determine the toxic and carcinogenic

potential of material IV are in progress, sponsored by the National Toxicology Program (1980). Previously published animal carcinogenicity studies of material IV reveal that it is capable of eliciting skin neoplasms in C57BL (9) but not in Swiss ICR (10) mice following chronic skin exposure. This is consistent with the present data in which skin tumors were not induced in C3H mice, which have previously been shown to be less sensitive to chemical skin carcinogenesis than C57BL/6 (2,11). In our opinion, the most significant occupational risk for material IV would be primary skin irritation and potential systemic toxicity associated with skin absorption. It is unlikely that chronic dermal exposures at concentrations above those used in the present experiment would be unnoticed by workers due to the irritant properties of this material.

The significance of the synergistic interaction between materials I, II, III, and VII, as it bears on potential occupational hazard, will depend upon a better understanding of mechanism. Studies are in progress in this and other laboratories to examine the hypothesis that material VII is a competitive inhibitor of epoxide hydrolase, the principal detoxification enzyme for DGEBA, the major component of materials I, II, and III (12). If material VII inhibits epoxide hydrolase, then reactive intermediates may accumulate as well as persist longer within the cell. In either case, the probability is increased that critical targets will be affected. The importance of this to the question of human risk can be investigated directly by comparing the levels of metabolites generated in parallel cultures of human and mouse skin following application of radiolabeled resins either singly or in combination. Assuming the original hypothesis is valid, then it

should be possible to compare both species in terms of whether risks are either comparable or substantially different, and, if different, the direction of the difference and its magnitude. The current observation of no or a very shallow dose response with the combined resin exposures is interpreted as a saturation phenomenon and thus is consistent with the enzymatic interaction hypothesis. An amount of material VII sufficient to achieve maximal steady-state levels of a reactive intermediate within epidermal cells may have been achieved at the lowest concentration in the current study. This raises the possibility that the absence of a carcinogenic effect of materials similar to I, II, and III applied singly is due to their slow rate of percutaneous absorption and their rapid detoxification. If this is true, then any modification that either increases penetration of the stratum corneum or decreases metabolism, e.g., by epoxide hydrolase, would presumably increase the potential carcinogenicity of these materials.

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## Appendix A

## CHEMICAL ANALYSES OF TEST MATERIALS

G. F. Dorsey, Development Division

The compositions and properties of the test materials were examined by liquid and gas chromatography, and gas chromatography/mass spectrometry, potentiometric titration, and vapor pressure osmometry.

Liquid and gas chromatography were the major chemical identification and quantification methods. Chromatographic procedures and techniques used were the result of consultation with, and a visit to, the analytical laboratories of Shell Development Company (Houston, Texas) and Dow Chemical Company (Freeport, Texas).

MATERIAL I

Diglycidyl ether of bisphenol A (DGEBA)

Celanese Coatings Epi-Rez 508

Lot MC8684

CAS no. 1675-54-3

Oligomer distribution: N = 0, 96%; N = 1, 1%; N = 2, 0

**Impurities:**

diol of DGEBA*	2%	epichlorohydrin	4 ppm
unidentified	1%	toluene	26 ppm
total chlorine	0.3%	methyl ethyl ketone	<50 ppm

phenyl glycidyl ether      220 ppm

additional very low-concentration impurities were noted but not identified

**Chemical/physical character:**

av. mol. wt.	362	epoxy equiv. wt.	168.0 g/equiv.
viscosity @ 25°C	4930 cps	density @ 25°C	1.16 g/cm <sup>3</sup>

\*2-[4-(2,3-dihydroxypropoxy)phenyl]-2-[4-(2,3-epoxypropoxy)phenyl]propane.

MATERIAL II

DGEBA

Shell Chemical Co. Epon 828

Lot 8WHJ17

CAS no. 1675-54-3

Oligomer distribution: N = 0, 78%; N = 1, 9%; N = 2, 2%

Impurities:

diol of DGEBA	4%	toluene	40 ppm
total chlorine	0.2%	methyl isobutyl ketone	40 ppm
epichlorohydrin	29 ppm	1,3-dichlorohydrin	15 ppm

additional low-concentration impurities were noted but not identified

Chemical/physical character:

av. mol. wt.	388	epoxy equiv. wt.	184.8 g/equiv.
viscosity @ 25°C	13,300 cps	density @ 25°C	1.16 g/cm³

MATERIAL III

DGEBA

Ciba-Geigy Araldite 6010

Lot BAP-427

CAS no. 1675-54-3

Oligomer distribution: N = 0, 78%; N = 1, 7%; N = 2, 2%

Impurities:

diol of DGEBA	4%	epichlorohydrin	3 ppm
total chlorine	0.3%	toluene	13 ppm
		1,3-dichlorohydrin	10 ppm

additional low-concentration impurities were noted but not identified

Chemical/physical character:

av. mol. wt.	390	epoxy equiv. wt.	184.6 g/equiv.
viscosity @ 25°C	13,320 cps	density @ 25°C	1.17 g/cm³

MATERIAL IV

Diglycidyl ether of resorcinol

Ciba-Geigy ERE 1359

Lot P6602

CAS no. 101-90-6

Oligomer/isomer total: estimated at 88%

Impurities:

total chlorine	1%	phenyl glycidyl ether	406 ppm
toluene	6000 ppm	toluene glycidyl ether	present
epichlorohydrin	845 ppm	monochlorohydrin	<10 ppm

several aromatic species containing oxygen were present

Chemical/physical character:

av. mol. wt.	257	epoxy equiv. wt.	124 g/eqiv.
viscosity @ 25°C	250 cps	density @ 25°C	1.21 g/cm <sup>3</sup>

MATERIAL V

N,N'-diglycidyl-5,5-dimethylhydantoin

Ciba-Geigy XB 2793

Lot BAR90786

CAS no. 15336-81-9

Oligomer/isomer total: estimated 89%

Impurities:

total chlorine	2.7%	toluene	<100 ppm
epichlorohydrin	1725 ppm	phenyl glycidyl ether	500 ppm

several aromatic species containing oxygen were present

Chemical/physical character:

av. mol. wt.	265	epoxy equiv. wt.	140.2 g/eqiv.
viscosity @ 25°C	177 cps	density @ 25°C	1.21 gm/cm <sup>3</sup>

MATERIAL VI

Diglycidyl ether of neopentyl glycol

Wilmington Chemicals Heloxy WC68

Lot GGG1367

CAS no. 17557-23-2

Oligomer/isomer total: estimated 70%

**Impurities:**

toluene	1%	total chlorine	4.6%
epichlorohydrin	none detected		

Pentyl moieties containing oxygen with molecular weights of 290, 310, 346, 402, and 440 were present

numerous unidentified low-boiling impurities were present in low concentrations

**Chemical/physical character:**

av. mol. wt.	250	epoxy equiv. wt.	136.6 g/equiv.
viscosity @ 25°C	16.1 cps	density @ 25°C	1.07 g/cm <sup>3</sup>

MATERIAL VII

*50% ERL-2258*

Bis(2,3-epoxycyclopentyl) ether

Union Carbide Chemicals and Plastics ERR 4205

CAS no. 2386-90-5

Oligomer/isomer total: ~97% (includes several isomeric forms)

**Impurities:**

low concentrations of structurally similar components such as 1-cyclopentene-3-one present, as well as other material containing carbonyl groups

**Chemical/physical character:**

av. mol. wt.	192	epoxy equiv. wt.	96.0 g/equiv.
viscosity @ 25°C	35 cps	density @ 25°C	1.17 g/cm <sup>3</sup>

MATERIAL VIII

Liquified meta-phenylenediamine

Applied Plastics Company Apcos 2330

Lot J7-017

CAS no. 108-45-2

Oligomer distribution: N = 0, 68%; N = 1 + N = 2, ~25%

Impurities:

oxygen	0.3%	sodium formate	400 ppm
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several small unidentified peaks observed in chromatographic analysis

Chemical/physical character:

av. mol. wt.	157	amine equiv. wt.	67.2 g/equiv.
viscosity @ 38°C	3250 cps	density @ 25°C	1.17 g/cm <sup>3</sup>

MATERIAL IX

Menthane diamine

Rohm and Haas

Lot G5783

CAS no. 80-52-4

Oligomer/isomer total: estimated 85%

Impurities:

All structurally similar: t-butylbenzene, hydroxy derivative of t-butylbenzene moiety, with 2-aminopropyl ion present; molecular weights of 182, 195, 333, respectively. Aromatic compounds with molecular weights of 272.

Chemical/physical character:

av. mol. wt.	172	amine equiv. wt.	93.3 g/equiv.
viscosity @ 25°C	13 cps	density @ 25°C	0.92 g/cm <sup>3</sup>

MATERIAL E<sup>a</sup>

DGEBA

Union Carbide Corporation

Lot 1742

Oligomer distribution:<sup>b</sup> N = 0, 85%; N = 1, 7%; N = 2, 1%Impurities:<sup>b</sup>

diol of DGEBA	1%	mesityl oxide	46 ppm
unidentified	1%	glycidol	30 ppm
epichlorohydrin	1476 ppm	2,3 dichlorohydrin	180 ppm
toluene	14 ppm	phenyl glycidyl ether	369 ppm

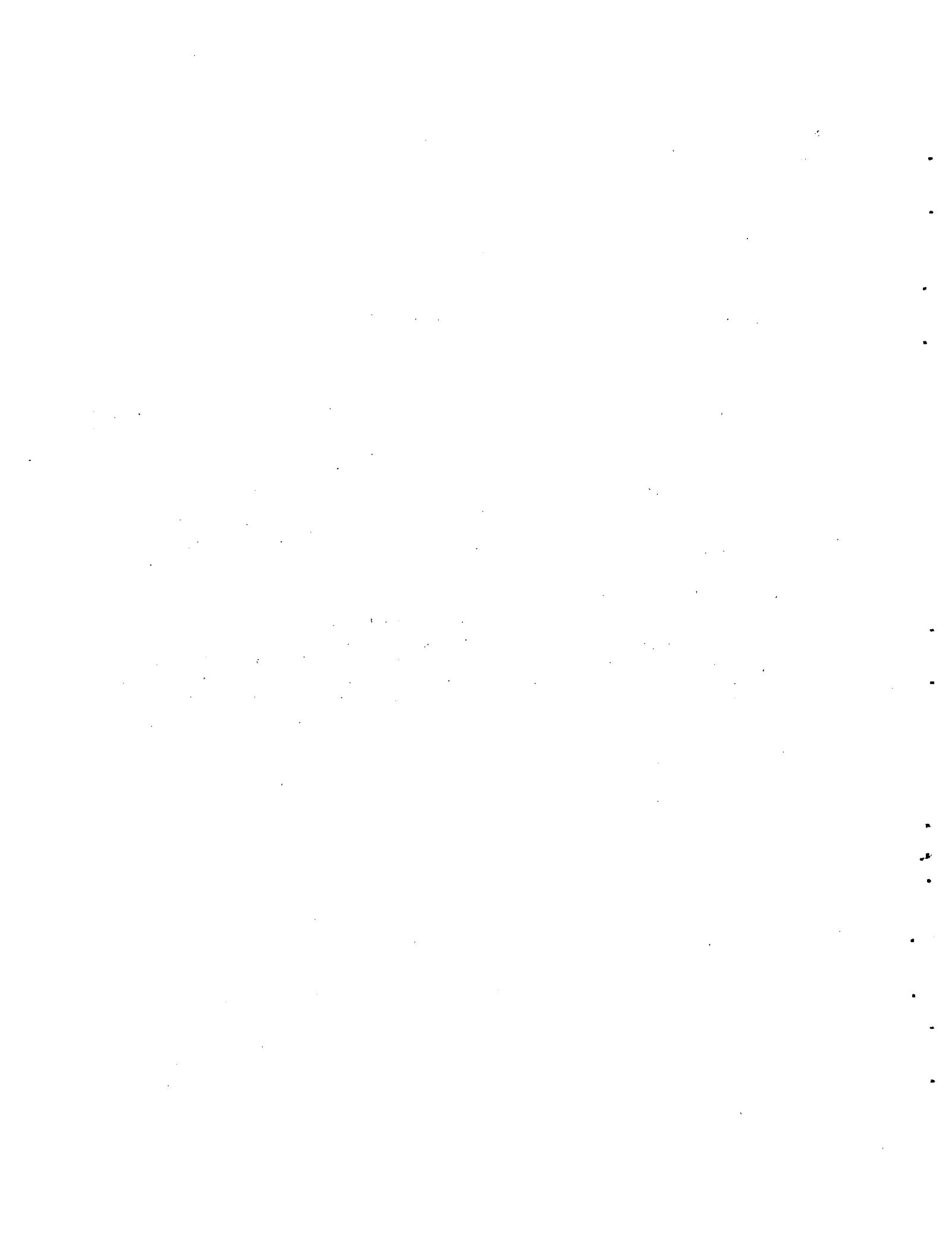
Chemical/physical character:<sup>c</sup>

av. mol. wt.	374	epoxy equiv. wt.	199 g/equiv.
viscosity @ 25°C	13,800 cps	density @ 25°C	1.16 g/cm <sup>3</sup>

<sup>a</sup>Material tested previously in experiments begun in 1975 and reported in ORNL 5375, where analysis indicated significant amounts (~10%) of an epoxidized polyglycol. Later analysis at Shell Development Company (Houston, Texas) indicated <5% 1,4-butanediol glycidyl ester was present in the resin. Analysis by Union Carbide Nuclear Division at the end of this test series did not show these materials to be present.

<sup>b</sup>1981 analysis.

<sup>c</sup>1978 analysis.



## Appendix B

## HEMATOLOGY AND BLOOD CHEMISTRY ANALYSES

C. A. Burtis, S. Garrett, E. M. Hall, E. L. Hurst, C. J. McDowell,  
J. M. Morton, and D. B. North, Health Division

Hematologic and blood chemistry analyses described in the text were performed in the clinical laboratory of the Health Division of the Oak Ridge National Laboratory.

## Hematology

Cell counting — Total red cell count and white cell count were determined for each specimen with a Model FN Coulter Counter (Coulter Electronics, Inc., Hialeah, Florida).

Hemoglobin analysis — The hemoglobin content of each sample was measured with a Coulter Hemoglobinometer (Coulter Electronics, Inc., Hialeah, Florida).

## Blood Chemistry

Total protein (TP), alkaline phosphatase (ALP), glutamic-oxalacetic transaminase (SGOT), glucose (GLU), triglycerides (TRIG), and blood urea nitrogen (BUN) were measured for each specimen with the miniature centrifugal analyzer that at the time of these studies was routinely operated in the clinical laboratory of the ORNL Health Division.

Analytical system — The centrifugal analyzer system used in these studies was developed and fabricated at the Oak Ridge National Laboratory and is a computer-controlled, multicuvet spectrophotometer (1,2) which utilizes a centrifugal field to simultaneously transfer and initiate several

individual reactions. These reactions subsequently proceed under identical conditions of time and temperature and are repetitively monitored as the cuvets spin through the analyzer's optical system. As a result, centrifugal analyzers generate a large quantity of time-absorbance data that may be either acquired, processed, and reduced in "real time" or stored for later processing by means of an integrated data system (3). In addition, a wide variety of computational algorithms are available (3) to calculate analytical results.

Reagents — Standard clinical chemical methods for determining BUN, GLU, TRIG, TP, ALP, and SGOT have been scaled down and adapted for use with the miniature analyzer. When available, commercial reagent kits were used in these studies.

For five of the assays Stat-Pak reagent kits were obtained from Calbiochem (San Diego, California). The two-vial kits were reconstituted by dissolving the contents of one vial with 2 ml of water or buffer, which was then added to and mixed with the contents of the second vial.

For the total protein assay, biuret reagent was prepared by dissolving 18 g CuSO<sub>4</sub>·5H<sub>2</sub>O, 9 g potassium-sodium tartrate, and 5 g potassium iodide in 700 ml of distilled water; 80-ml of 50% NaOH was then added, and the volume was adjusted to 1 liter.

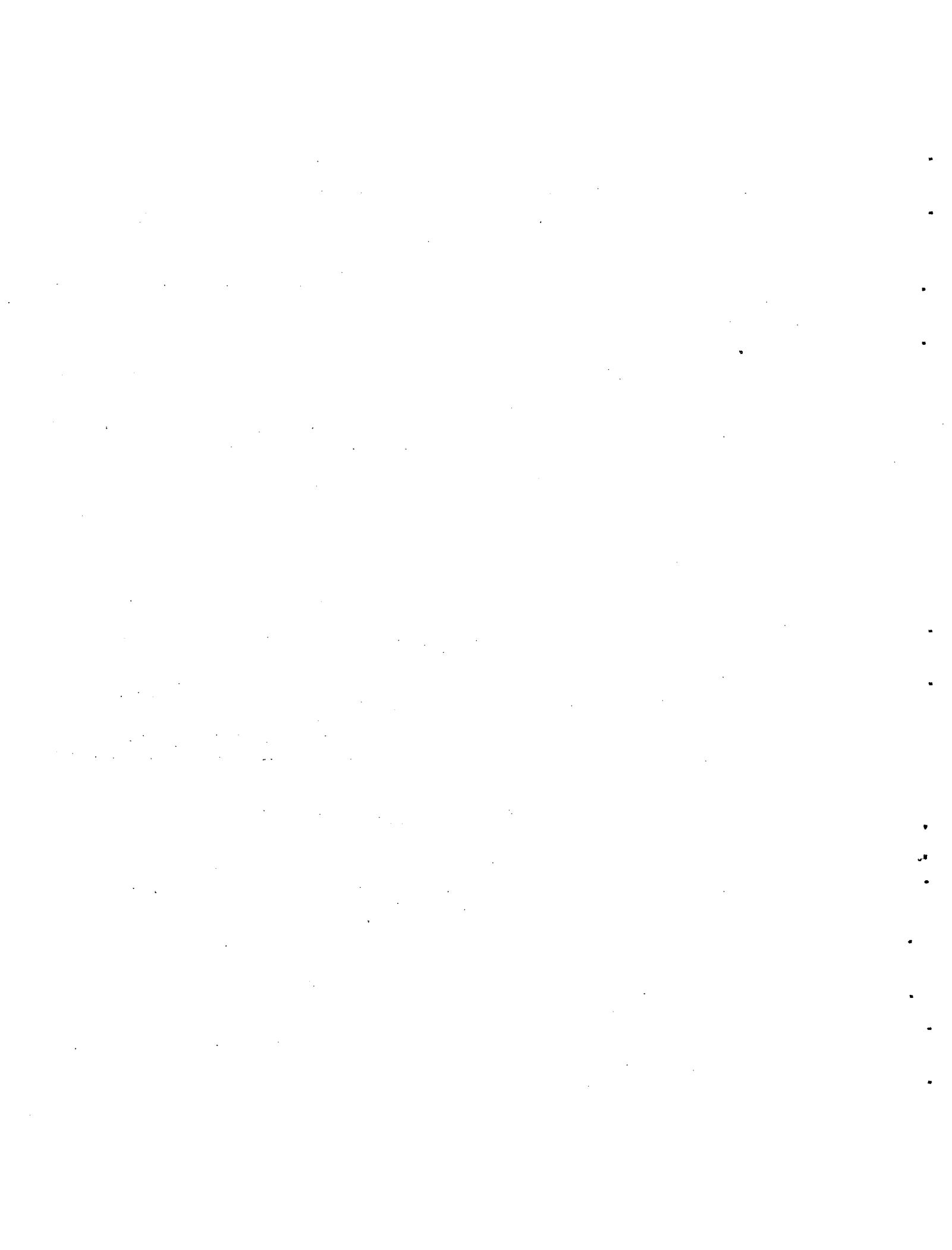
Procedures — The procedures for the individual determinations have been described previously (2). The pertinent analytical parameters are summarized in Table B-1. For each rotor analyzed, three quality control samples were assayed, and their results were evaluated statistically to validate the results.

Table B-1. Analytical parameters for clinical methods adapted for use with the centrifugal analyzer

Procedure	Volume ( $\mu$ l)		Wavelength (nm)	Reaction type	Reference
	Sample	Total			
<b>Enzyme</b>					
ALP	10	130	405	rate	4
SGOT	20	130	340	rate	5
<b>Metabolites</b>					
BUN	2	122	340	rate ratiometric	6
GLU	2	122	340	equilibrium	7
TP	3	123	540	equilibrium	8
TRIG	4	124	340	equilibrium	9

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## Appendix C

## Statistical Analysis of Mortality and Relative Skin Carcinogenicity

D. A. Wolf and T. J. Mitchell, Computer Sciences Division

## Systemic Mortality

For the statistical test of systemic mortality (text Table 5), the event of interest was time to death from causes other than skin tumor. Since cause of death was not routinely recorded, we treated the occurrence of a skin tumor as a censoring mechanism, i.e., the only information drawn from skin tumor-bearing animals was that the event of interest occurred (or would have occurred but for sacrifice or death related to skin tumor) later than the appearance of the skin tumor. To avoid bias, it was also necessary to assume that the censoring was "nonprognostic" (1) in that skin tumor incidence did not select either for or against animals that would otherwise have died of another cause at a given later time.

Under these assumptions, we used the standard log-rank test (2) to compare the force of non-skin tumor mortality in each treated group with that of the acetone control. (This test can also be viewed as a special case of the Mantel-Haenszel (3) test familiar to many biologists.) The test statistic, approximately distributed as a chi-squared under the hypothesis of identical time-dependent force of non-skin tumor mortality in both groups, is given in text Table 5A and B.

## Tumor-Related Mortality

To investigate the effect of the presence of skin tumor on the force of mortality in each group, we again used a variation of the Mantel-Haenszel

test. Just prior to the ith "natural" death (i.e., excluding sacrifices), there are  $TF_i$  skin tumor-free animals and  $TB_i$  skin tumor-bearing animals. ("Tied" deaths were ordered arbitrarily. Deaths precede sacrifices in case of ties.) Under the null hypothesis that presence of skin tumor has no effect on the force of mortality, the probability that the ith natural death comes from the tumor-bearing group is  $p_i = TB_i / (TB_i + TF_i)$ . Let  $X_i = 1$  if this event is observed and  $X_i = 0$  otherwise; then  $X_i$  is a Bernoulli random variable with mean  $p_i$  and variance  $v_i = p_i(1 - p_i)$ . For the purpose of making inferences about the force of mortality, it is appropriate to consider  $TB_i$  and  $TF_i$  as fixed for each  $i$ , so the  $X_i$  are treated as independent random variables. The sum  $X = \sum X_i$ , summed over the deaths when there were animals at risk with and without tumors, has mean  $p = \sum p_i$  and variance  $v = \sum v_i$ . Because of the central limit effect of summing several variables, the statistic  $\phi = (X - p)^2/v$  is approximately distributed under the null hypothesis as chi-squared with one degree of freedom. In cases where fewer than 9  $X_i$ 's contributed to the sum or where  $P < 2$ , we found this approximation to be poor, so we ignored the chi-squared values.

It should be noted that the power of this test (and the test for systemic mortality described above) depends on the number and classification of the animals at risk prior to each death and also on the behavior of the relative forces of mortality. If, for example, the presence of a tumor decreases the force of mortality early in life and increases it later,  $\phi$  will likely be too small to be declared "significant." The correct interpretation for a non-significant test is therefore "inconclusive" rather than "no difference."

### Relative Potency

The potency of a test material relative to a standard is defined as the ratio of doses, standard/test, that elicit equivalent effects (4). The standard was B(a)P and the test materials were the epoxy resins. Median time to tumor, T<sub>50</sub>, was the effect. Each relative potency calculation used only data from a single test material (at several doses) and from the appropriate B(a)P dose groups. Males and females were considered separately because of the noticeably greater tumor incidence in males. The  $\chi^2$  for the log-rank test (with 1 degree of freedom) of the hypothesis of no sex difference with respect to tumor response (2) are given in Table C-1. The inverses of the estimated relative potencies and their confidence limits are reported in text Table 9.

To estimate T<sub>50</sub>, the distribution of time (T) from first treatment to first skin tumor was modelled by use of a Weibull distribution with shape, location, and scale parameters k, w, and b, respectively. The three-parameter Weibull distribution can be characterized by the cumulative distribution function  $F(t) = 1 - \exp[-b(t - w)^k]$  for  $k, b > 0$  and  $t > w$ . T<sub>50</sub> is therefore given by

$$T_{50} = w + (0.69315/b)^{1/k}. \quad (1)$$

If k and w are the same for the standard and test materials, then any two doses that are equivalent in terms of T<sub>50</sub> are also equivalent in terms of b by Eq. (1). Relative potency in terms of T<sub>50</sub> can therefore be calculated equivalently in terms of b. The subsequent estimate of the standard error of

Table C-1. Sex effect on time to tumor distribution

Material	Dose (mg/week)	Observed/Expected <sup>a</sup>		$\chi^2$ for log-rank test <sup>b</sup>
		Females	Males	
V	3.75	16/23.05	24/16.95	5.09*
	1.87	18/24.10	22/15.90	3.88*
	0.94	12/15.7	15/11.30	2.08
VI	3.75	1/5.01	9/4.99	6.43*
	1.87	2/2.85	4/3.15	0.49
VII	75	3/1.97	2/3.03	0.88
X	0.0150	44/45.33	48/46.67	0.08
	0.0075	45/54.99	50/40.01	4.31*
	0.0038	16/23.10	26/18.09	4.85*
	0.0019	2/1.71	2/2.29	0.09
XI <sup>c</sup>	0.150	40/32.97	40/47.03	2.55
	0.015	31/35.63	38/33.37	1.25
A	75	10/15.12	15/9.98	4.21*
	37.5	11/10.09	10/10.91	0.16
	18.75	8/10.00	10/8.00	0.90
B	3.75	20/27.00	22/15.00	5.09*
	1.87	20/17.10	22/24.90	0.83
	0.94	16/22.99	21/14.01	5.62*
C	75	6/8.17	10/7.83	1.18
	37.5	14/15.23	20/18.77	0.18
	18.75	10/14.76	17/12.24	3.38
D	75	9/12.03	14/10.97	1.6
	37.5	3/7.11	10/5.89	5.24*
	18.75	1/7.16	13/6.84	10.84**
E <sup>d</sup>	75	17/28.33	28/16.67	12.24**
	15	6/11.11	13/7.89	5.65*

<sup>a</sup>(Observed number of tumors)/(expected number of tumors if no differences in time-to-tumor distributions).

<sup>b</sup>\*P < 0.05; \*\*P < 0.001.

<sup>c</sup>B(a)P from an earlier experiment tested concurrently with materials VII and E.

<sup>d</sup>Mixture of material VII and Union Carbide DGEBA tested in an earlier experiment.

relative potency is not only simpler but requires fewer dubious approximations than would be needed if k and w were allowed to differ between materials. The assumption of common k and w is therefore a standard part of our estimation procedure. A statistical check on the validity of this assumption is indicated below. For further commentary on the practice of "fixing" k and w, see Peto and Lee (5) or Peto et al. (6).

The method of maximum likelihood was used to estimate the Weibull parameters. Common k and w but individual b's were estimated for each dose of test material and standard. In calculating the likelihood, all observations were used, including the times to death of animals that die before tumor occurrence. In such cases, the time to tumor is considered to be "right-censored" in that it can only be inferred that the time to tumor exceeds the time to death. The censoring mechanism (death) is assumed to be "nonprognostic" (1), i.e., death does not select either for or against animals which would otherwise be "destined" to get a tumor at a given subsequent time.

The maximum likelihood calculations were made with a computer program kindly provided by Dr. D. G. Thomas of the National Cancer Institute. This program was also used to calculate T50 and its standard error, based on the Weibull fit. The results are summarized in Table C-2A and B. The estimates of the Weibull parameters have large variances and are highly correlated, so their individual values are difficult to interpret, whereas the T50 values and their approximate standard errors are fairly stable. Note that the estimates of T50 for the standard treatment [B(a)P] groups differ slightly

Table C-2. Summary of Weibull fits

Parameters and material	Dose (mg/week)	No. of animals	Tumor- bearing animals	b (Weibull)	T50 (SE)
<u>A. FEMALES</u>					
$k = 6.862$					
$w = 76.068$					
X	0.015 0.0075 0.0038 0.0019	45 50 50 50	44 45 16 2	2.64420E-17 6.27310E-19 2.04230E-20 2.23850E-21	323 (6.0) 502 (10.0) 778 (26.1) 1044 (109.0)
V	3.75 1.87 0.94	25 25 25	16 18 12	1.65170E-19 8.54700E-20 4.25680E-20	593 (18.9) 646 (19.8) 706 (26.5)
$k = 4.645$					
$w = 157.417$					
X	0.015 0.0075 0.0038 0.0019	45 50 50 50	44 45 16 2	3.54600E-11 1.30000E-12 6.56690E-14 7.32790E-15	322 (5.8) 492 (11.8) 794 (35.6) 1178 (175.6)
VI	3.75 1.87	25 25	1 2	7.18390E-15 1.87920E-14	1183 (236.3) 991 (135.6)
$k = 6.927$					
$w = 66.011$					
VI <sup>a</sup>	0.15 0.015	40 40	40 31	4.61890E-13 4.84760E-17	123 (1.5) 281 (5.9)
VII	75	40	3	3.37810E-21	922 (84.0)
$k = 5.381$					
$w = 131.718$					
X	0.015 0.0075 0.0038 0.0019	45 50 50 50	44 45 16 2	3.72710E-13 1.14120E-14 4.87350E-16 5.40160E-17	322 (5.8) 496 (10.9) 787 (31.3) 1117 (142.7)
A	75 37.5 18.75	25 25 25	10 11 8	6.53400E-16 8.25540E-16 5.56200E-16	752 (36.8) 726 (33.3) 771 (42.7)

(Table C-2 continued)

Table C-2 (continued)

Parameters and material	Dose (mg/week)	No. of animals	Tumor- bearing animals	b (Weibull)	T50 (SE)
$k = 6.296$					
$w = 97.996$					
X	0.015	45	44	1.07630E-15	323 (5.9)
	0.0075	50	45	2.77170E-17	500 (10.2)
	0.0038	50	16	9.91220E-19	780 (27.7)
	0.0019	50	2	1.09070E-19	1067 (118.2)
B	3.75	25	20	7.55850E-18	592 (17.9)
	1.87	25	20	9.74110E-18	573 (17.0)
	0.94	25	16	2.99020E-18	671 (22.8)
$k = 5.72$					
$w = 116.513$					
X	0.015	45	44	4.05190E-14	322 (5.9)
	0.0075	50	45	1.19490E-15	497 (10.8)
	0.0038	50	16	4.81490E-17	784 (30.0)
	0.0019	50	2	5.32340E-18	1098 (134.3)
C	75	25	6	4.34580E-17	796 (49.8)
	37.5	25	14	1.24620E-16	682 (26.4)
	18.75	25	10	6.92920E-17	743 (35.0)
$k = 5.233$					
$w = 137.471$					
X	0.015	45	44	9.53300E-13	322 (5.8)
	0.0075	50	45	3.00000E-14	496 (11.2)
	0.0038	50	16	1.32010E-15	788 (32.1)
	0.0019	50	2	1.46490E-16	1128 (149.8)
D	75	25	9	1.44920E-15	776 (41.4)
	37.5	25	3	5.30410E-16	912 (90.3)
	18.75	25	1	1.61250E-16	1110 (197.4)
$k = 7.69$					
$w = 59.274$					
X <sup>a</sup>	0.15	40	40	8.91250E-15	123 (1.5)
	0.015	40	31	6.11800E-19	282 (5.4)
E <sup>b</sup>	75	40	17	1.13780E-22	740 (21.7)
	15	39	6	3.71330E-23	846 (45.7)

(Table C-2 continued)

Table C-2 (continued)

Parameters and material	Dose (mg/week)	No. of animals	Tumor- bearing animals	b (Weibull)	T50 (SE)
<b>B. MALES</b>					
$k = 6.262$					
$w = 64.339$					
X	0.015	50	48	6.20320E-16	317 (6.3)
	0.0075	50	50	3.55700E-17	464 (9.5)
	0.0038	45	26	1.76160E-18	710 (20.2)
	0.0019	50	2	7.96000E-20	1123 (129.3)
V	3.75	25	24	1.15900E-17	542 (16.2)
	1.87	25	22	6.60070E-18	587 (18.2)
	0.94	25	15	3.09470E-18	654 (24.4)
$k = 6.601$					
$w = 46.567$					
X	0.015	50	48	6.10470E-17	317 (6.5)
	0.0075	50	50	3.46500E-18	465 (9.8)
	0.0038	45	26	1.63920E-19	710 (19.7)
	0.0019	50	2	7.35120E-21	1109 (129.4)
VI	3.75	25	9	8.38980E-20	781 (37.8)
	1.87	25	4	3.68580E-20	879 (66.7)
$k = 9.909$					
$w = 0.635$					
XI <sup>a</sup>	0.15	40	40	9.24870E-22	128 (2.3)
	0.015	40	38	5.01140E-25	274 (5.0)
VII	75	40	2	2.67190E-30	931 (81.5)
$k = 6.699$					
$w = 45.103$					
X	0.015	50	48	3.35920E-17	318 (6.4)
	0.0075	50	50	1.84860E-18	465 (9.6)
	0.0038	45	26	8.49830E-20	710 (19.5)
	0.0019	50	2	3.79670E-21	1103 (123.5)
A	75	25	15	1.27840E-19	671 (24.1)
	37.5	25	10	6.47210E-20	738 (32.9)
	18.75	25	10	8.00940E-20	716 (31.7)

(Table C-2 continued)

Table C-2 (continued)

Parameters and material	Dose (mg/week)	No. of animals	Tumor- bearing animals	b (Weibull)	T50 (SE)
<b>k = 7.857</b>					
<b>w = 0.584</b>					
X	0.015	50	48	1.51280E-20	318 (6.5)
	0.0075	50	50	7.24660E-22	468 (8.9)
	0.0038	45	26	2.72260E-23	711 (17.8)
	0.0019	50	2	1.18150E-24	1060 (103.3)
B	3.75	25	22	2.30290E-22	542 (15.1)
	1.87	25	22	1.07420E-22	597 (16.5)
	0.94	25	21	8.86690E-23	612 (17.5)
<b>k = 7.678</b>					
<b>w = 3.148</b>					
X	0.015	50	48	4.58950E-20	318 (6.5)
	0.0075	50	50	2.31300E-21	468 (9.2)
	0.0038	45	26	9.11450E-23	711 (18.1)
	0.0019	50	2	3.97960E-24	1067 (107.1)
C	75	25	10	7.49580E-23	729 (30.0)
	37.5	25	20	1.54260E-22	664 (19.5)
	18.75	25	17	1.40360E-22	672 (21.3)
<b>k = 7.782</b>					
<b>w = 0.191</b>					
X	0.015	50	48	2.32900E-20	318 (6.4)
	0.0075	50	50	1.15140E-21	468 (9.2)
	0.0038	45	26	4.43990E-23	711 (17.9)
	0.0019	50	2	1.93290E-24	1063 (105.9)
D	75	25	14	4.43820E-23	711 (24.4)
	37.5	25	10	3.86160E-23	724 (29.5)
	18.75	25	13	3.74190E-23	727 (25.9)
<b>k = 8.054</b>					
<b>w = 22.244</b>					
XI <sup>a</sup>	0.15	40	40	3.45550E-17	128 (2.4)
	0.015	40	38	3.45080E-20	272 (5.2)
E <sup>b</sup>	75	40	28	1.98870E-23	652 (15.2)
	15	40	13	7.55790E-24	732 (24.7)

<sup>a</sup>B(a)P from an earlier experiment tested concurrently with materials VII and E.

<sup>b</sup>Mixture of material VII and Union Carbide DGEBA tested in an earlier experiment.

from one comparison to another. This occurs because the comparison with B(a)P was made independently for each test material, and a different k and w were estimated each time.

The next step in the relative potency calculations involved fitting the following equation to the logarithm of the b's:

$$\log_{10} b = a_i + c_i \log_{10} \text{dose}, \quad (2)$$

where i = test or std. This was done by the method of least squares, applied to the b's; the maximum likelihood estimates of the b's were obtained as described above. The weight used for each b was the number of tumors observed in that treatment group. These weights were derived by noting that, for fixed k and w, the variance of the common logarithm of b is approximately the same as 0.189 times the inverse of the number of tumors. Actually, k and w (though common to all groups within an assay) are not fixed; however, the differences among the logarithms of the b's are fairly stable with respect to variations of k and w (5). The effect of such variations would therefore be to raise or lower  $a_i$  in Eq. (2) by roughly a constant amount; this would have little or no effect on the relative potency in Eq. (3) below. [In the future, we plan to estimate the coefficients in Eq. (2) directly by maximum likelihood, thus avoiding the weighted least-squares approach altogether.]

The least-squares results are given in Table C-3.

Table C-3. Weighted least-squares results,  $\log_{10} b = a_1 + c_1 \log_{10}$  dose

Material	Sex	a <sub>test</sub>	c <sub>test</sub>	a <sub>std</sub>	c <sub>std</sub>	SSE <sup>a</sup>	DF <sup>a</sup>
V, X	F	-19.34	0.9780	- 7.380	5.065	0.8289	3
	M	-17.464	0.9414	- 7.474	4.233	0.0707	3
VI, X	F	-13.35	-1.3820	- 2.3184	4.4780	0.4902	2
	M	-19.75	1.182	- 8.412	4.270	0.0589	2
VII, XI <sup>b</sup>	F	-20.47	-	- 9.06	3.979	-	0
	M	-29.57	-	-18.343	3.266	-	0
A, X	F	-15.32	0.0969	- 3.871	4.713	0.7534	3
	M	-19.64	0.3752	- 8.597	4.311	0.3203	3
B, X	F	-17.38	0.6264	- 5.984	4.948	2.015	3
	M	-22.08	0.6938	-11.52	4.541	0.3003	3
C, X	F	-15.78	-0.1937	- 4.721	4.775	1.560	3
	M	-21.30	-0.385	-11.16	4.474	0.4356	3
D, X	F	-17.71	1.535	- 3.533	4.675	0.6106	3
	M	-22.59	0.1239	-11.41	4.502	0.0900	3
E, <sup>c</sup> XI <sup>b</sup>	F	-23.25	0.6957	-10.62	4.163	-	0
	M	-23.83	0.6011	-13.99	3.001	-	0

<sup>a</sup>SSE is the weighted residual sum of squares. If the fitted model is adequate, SSE/0.189 is approximately distributed as chi-squared with DF degrees of freedom.

<sup>b</sup>B(a)P from an earlier experiment tested concurrently with materials VII and E.

<sup>c</sup>Mixture of material VII and Union Carbide DGEBA tested in an earlier experiment.

Upon completion of the least-squares estimation of Eq. (2), the relative potency at the dosage of the test material,  $d_{test}$ , can be calculated by solving for the dosage of the standard,  $d_{std}$ , which is predicted to yield the same  $b$  as  $d_{test}$ . The ratio  $d_{std}/d_{test}$  is the relative potency. The common logarithm of this ratio is given by:

$$\log_{10} (\text{relative potency at } d_{test})$$

$$= \frac{(a_{test} - a_{std}) + (c_{test} - c_{std})\log_{10} d_{test}}{c_{std}} \quad (3)$$

It can be seen from Eq. (3) that relative potency does depend upon  $d_{test}$  when  $c_{test} \neq c_{std}$ . It was quite clear that this was the case for the data presented in this report. An upper 95% confidence limit for the ratio of Eq. (3) was obtained by applying Fieller's theorem (4). Taking antilogs of Eq. (3) and of this confidence limit gives the relative potency estimate and its confidence limit, the inverses of which are given in text Table 9 for each assay.

It is evident that the relative potency calculations rest on a series of statistical assumptions:

- (i) the adequacy of the Weibull model,
- (ii) the assumption of nonprognostic censoring,
- (iii) the assumption of common  $(k, w)$  in each assay,
- (iv) the appropriateness of the weighted least-squares procedure,  
particularly the rule for assigning weights,
- (v) the adequacy of the regression model, Eq. (2).

Statistical tests were made for (iii) and (v). In the case of assumption (iii), the NCI program was used to maximize the likelihood when this assumption is dropped. The ratio  $\psi$  of this maximum likelihood to that obtained when the assumption is enforced provides a likelihood ratio test for the validity of the assumption. Twice the natural logarithm of  $\psi$  is approximately distributed as chi-squared with  $2(n_G - 1)$  degrees of freedom, where  $n_G$  is the number of groups in the assay. The results are given in the third column of Table C-4. It is disturbing that in four cases (all male) there is strong statistical evidence that assumption (iii) does not hold. However,  $(k, w)$  did not differ significantly among the dose groups of the standard [B(a)P]. We therefore used the following alternative procedure to estimate relative potency for the four cases in which assumption (iii) was rejected. Assuming that  $(k, w)$  is constant within the standard dose groups, we used Eq. (1) and (2) (for  $i = \text{std}$  only) to obtain T50 as a function of dose for the standard. For each dose of the test material, T50 was obtained from the Weibull parameters based on data from that dose group only. We were then able to calculate the equivalent dose of the standard, from which the relative potency followed. This alternative calculation yielded relative potencies that were within the one-sided confidence intervals given in text Table 9 in all cases except Material VII, for which no confidence interval was calculated. We tentatively conclude that although violations of assumption (iii) may occur, they do not seriously affect the results given here.

Assumption (v) was tested by comparison of the weighted SSE from the least-squares analysis with the theoretical variance (0.189). The chi-squared statistic and its degrees of freedom are given in the fourth

Table C-4. Test of assumptions

Material	Sex	$\chi^2$ (DF) for log-rank test, <sup>a</sup> common k and w	$\chi^2$ (DF) for adequacy of linear model <sup>a</sup>
V	F	22.640 (12)*	4.39 (3)
	M	10.816 (12)	0.37 (3)
VI	<u>F</u> <sup>b,c</sup>	10.198 (10)	2.60 (2)
	<u>M</u> <sup>b,c</sup>	14.878 (10)	0.31 (2)
VII	<u>F</u> <sup>b</sup>	7.134 (4)	no test
	<u>M</u> <sup>b</sup>	13.734 (4)**	no test
A	F	11.624 (12)	3.99 (3)
	M	29.992 (12)**	1.70 (3)
B	F	14.956 (12)	10.68 (3)*
	M	15.687 (12)	1.59 (8)
C	F	13.125 (12)	8.27 (3)*
	M	12.358 (12)	2.31 (3)
D	<u>F</u> <sup>a,b</sup>	16.622 (12)	3.24 (3)
	M	45.107 (12)***	0.48 (3)

<sup>a</sup>\*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001.<sup>b</sup>Dose group(s) with 0 and/or 1 tumor.<sup>c</sup>Average number of tumors per dose fewer than five.

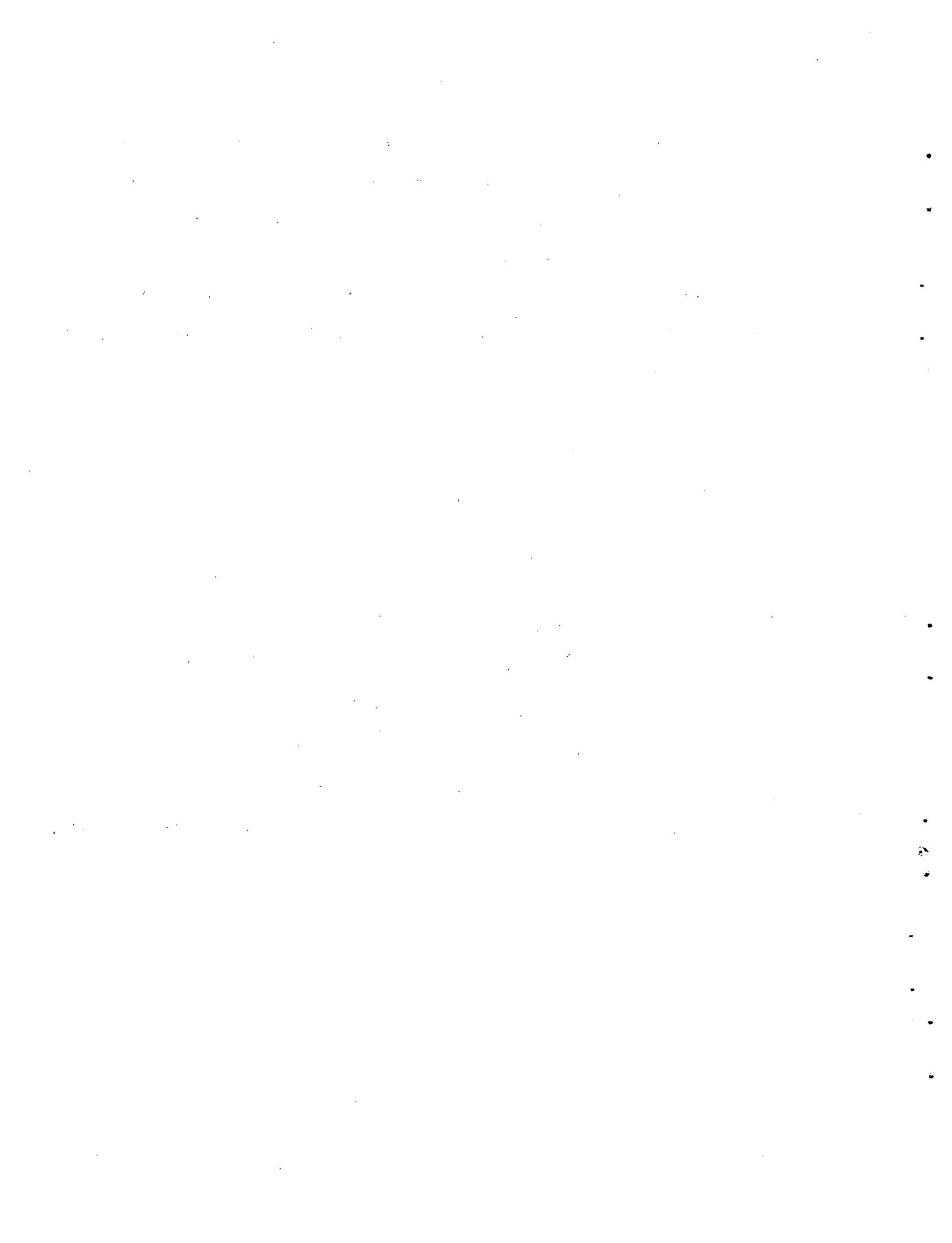
column of Table C-4. In column 2 of the same table are indicated those test materials with an average of fewer than five tumors per dose group or fewer than two tumors in any single dose group. These can be considered warning "flags" that assumption (iv) may be shaky.

The validity of assumption (i) can be evaluated visually in text Fig. 2. [Note that the Weibull curves there are also based on assumption (iii).] We have made no attempt to use statistical models other than the Weibull for time-to-tumor distributions.

Assumption (ii) is intuitively reasonable, but is not statistically testable.

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Appendix D

Animal Data

Key for data on following pages:

1st line - Material, sex, dose

2nd line - Identification no. (ID), age at first painting (AFP), time  
to first tumor (T), removal code (D), age at death (AAD)

I F 75				0601 66 . D 621 0205 71 . D 682			
ID	AFP	T	D AAD	0701 78 . D 703 0305 71 . D 708	0604 66 . D 717 0403 71 . D 708	0903 70 . D 739 0405 71 . D 730	0901 70 . D 750 1304 71 . D 747
1105	71	.	D 199	1401 71 . D 751 0303 71 . D 760	1001 71 . D 768 0301 71 . D 782	0805 71 . D 771 1205 71 . D 782	0804 71 . D 778 0402 71 . D 785
0304	71	.	D 436	0902 70 . D 784 0404 71 . D 785	1103 71 . D 652 0602 66 . D 783 1202 71 . D 785	1302 71 . D 655 1405 71 . D 793 0102 66 . D 784	0505 71 . D 690 1402 71 . D 794 1204 71 . D 795
0203	71	.	D 465	0603 66 . S 803 1305 71 . D 795	0401 71 . D 698 0605 72 . S 809 0203 71 . D 802	0104 73 . D 705 1403 71 . S 810 1101 71 . D 803	0102 73 . D 717 1404 71 . S 810 1102 71 . S 803
0305	71	.	D 582	1501 71 . S 810 1103 71 . S 803	0102 73 . D 735 1502 71 . S 810 1105 71 . S 803	1303 71 . D 736 1503 71 . S 810 1203 71 . S 803	1101 71 . D 750 1504 71 . S 810 1302 71 . S 803
0101	73	.	D 595	1505 71 . S 810 1303 71 . S 803	0202 71 . D 761 1505 71 . S 810 1303 71 . S 803	0201 71 . D 766 1002 71 . S 816 0302 71 . D 806	0201 71 . D 770 1004 71 . S 816 0103 66 . S 805
0404	71	.	D 773	1005 71 . S 816 0104 66 . S 805	0501 71 . D 780 1601 71 . S 820 0105 66 . S 805	0405 71 . D 801 1602 71 . S 820 0501 71 . S 814	1203 71 . S 803 1603 71 . S 820 0503 71 . S 814
1201	71	.	D 611	1604 71 . S 820 0504 71 . S 814	1204 71 . S 803 1605 71 . S 820 0505 71 . S 814	1205 71 . S 803 0802 71 . S 821 0204 71 . D 816	1301 71 . S 803 0803 71 . S 822 0201 71 . S 828
0504	71	.	D 617	0904 70 . S 822 0202 71 . S 828	0404 71 . S 807 0905 70 . S 822 II M 75	0502 71 . S 807 0702 78 . S 835 ID AFP T D AAD	0503 71 . S 807 0703 78 . S 835 II F 75
0103	73	.	D 795	0704 78 . S 835	1102 71 . S 813 0705 78 . S 835 0605 70 . D 528	0103 73 . S 810 0704 78 . S 835 1604 71 . D 571	1104 71 . S 813 II ID AFP T D AAD 0904 70 . D 610
1104	71	.	D 596	0204 71 . S 814 0705 78 . S 835 0705 71 . D 626	0204 71 . S 814 0705 78 . S 835 0905 70 . D 686	0205 71 . S 814 0905 70 . D 686	0205 71 . S 814 0905 70 . D 686
0301	71	.	D 661	0301 71 . S 814 0101 66 . D 549 1504 71 . D 712	0303 71 . S 814 0401 71 . D 556 0602 70 . D 756	0502 71 . D 659 1104 71 . S 596 0902 70 . D 792	0502 71 . D 659 1104 71 . S 596 0902 70 . D 792
0303	71	.	D 661	1201 71 . D 661 1504 71 . D 712	0304 71 . D 610 0803 71 . D 793	1301 71 . D 680 1004 71 . D 793	1301 71 . D 680 1004 71 . D 793
1003	71	.	D 568	1603 71 . D 800	0502 71 . D 659 1004 71 . D 793	0601 70 . D 805	0601 70 . D 805
0901	71	.	D 607	0601 70 . D 805	1201 71 . D 661 1603 71 . D 800	1301 71 . D 680 0601 70 . D 805	1301 71 . D 680 0601 70 . D 805

0603	70	.	S	807	0302	71	.	D	775	1404	71	.	S	810
0604	70	.	S	807	1302	71	.	D	778	1405	71	.	S	810
0701	71	.	S	814	1102	71	.	D	783	1004	71	.	D	811
0702	71	.	S	814	1202	71	.	D	787	0601	70	.	D	812
0703	71	.	S	814	0303	71	.	D	792	0602	70	.	S	812
0704	71	.	S	814	0502	71	.	D	794	0603	70	.	S	812
1001	71	.	S	815	1103	71	.	S	800	0605	70	.	S	812
1002	71	.	S	815	1104	71	.	S	800	1501	71	.	S	815
1003	71	.	S	815	0404	71	.	D	801	1502	71	.	S	815
1005	71	.	S	815	0301	71	.	S	807	1503	71	.	S	815
1501	71	.	S	815	0304	71	.	S	807	1504	71	.	S	815
1502	71	.	S	815	0403	71	.	S	807	1003	71	.	S	822
1503	71	.	S	815	0405	71	.	S	807	1005	71	.	S	822
1505	71	.	S	815	1203	71	.	S	808	0904	71	.	D	828
1601	71	.	S	815	1205	71	.	S	808	0901	71	.	S	835
1602	71	.	S	815	0101	80	.	D	818	0902	71	.	S	835
1605	71	.	S	815	0102	80	.	S	818	0903	71	.	S	835
1401	71	.	S	816	0103	80	.	S	818	0905	71	.	S	835
1402	71	.	S	816	0105	80	.	S	818					
1403	71	.	S	816	1304	71	.	S	813	IV		F		1.8
1404	71	.	S	816	1305	71	.	S	813	ID	AFP	T	D	AAD
1405	71	.	S	816	0503	71	.	S	814					
0801	71	.	S	821	0202	78	.	D	821	0404	70	.	D	457
0901	70	.	D	821						0202	78	.	D	472
0802	71	.	S	822	III	M				0403	70	.	D	534
0804	71	.	S	822	ID	AFP	T	D	AAD	0103	71	.	D	536
0805	71	.	S	822						0502	71	.	D	579
0903	70	.	S	822	1604	71	.	S	124	0505	71	.	D	596
					1403	71	.	D	142	0302	71	.	D	605
III		F			1402	71	.	D	472	0504	71	.	D	662
ID	AFP	T	D	AAD	0604	70	.	D	627	0204	78	.	D	673
					1605	71	.	D	633	0301	71	.	D	689
0401	71	.	D	526	1505	71	.	D	689	0501	71	.	D	695
0402	71	.	D	584	0702	69	.	D	689	0102	71	.	D	704
0204	78	.	D	605	1002	71	.	D	694	0303	71	.	D	710
1201	71	.	D	626	1001	71	.	D	696	0503	71	.	D	718
0203	78	.	D	676	0705	69	.	D	777	0405	70	.	D	721
0201	78	.	D	722	0801	71	.	D	799	0101	71	.	D	736
1204	71	.	D	725	0704	69	.	D	800	0401	70	.	S	743
0305	71	.	D	729	1601	71	.	S	807	0402	70	.	S	743
0501	71	.	D	730	1602	71	.	S	807	0205	78	.	D	752
0205	78	.	D	737	1603	71	.	S	807	0104	71	.	D	746
1101	71	.	D	732	0802	71	.	S	808	0105	71	.	D	746
1105	71	.	D	740	0803	71	.	S	808	0304	71	.	D	747
0505	71	.	D	745	0804	71	.	S	808	0305	71	.	S	751
1303	71	.	D	745	0805	71	.	S	808	0201	78	.	D	764
0104	80	.	D	769	0701	69	.	S	807	0203	78	.	D	764
1301	71	.	D	761	0703	69	.	S	807					
0504	71	.	D	771	1401	71	.	S	810					

IV F 0.9				2501	71	.	S 816	2005	71	.	D 785
ID	AFP	T	D AAD	2502	71	.	S 816	2001	71	.	S 803
1505	71	.	D 540	2503	71	.	S 816	2002	71	.	S 803
1503	71	.	D 563	2101	71	.	S 817	2003	71	.	S 803
1305	71	.	D 571	2103	71	.	S 817	1701	71	.	S 809
1201	78	.	D 627	2104	71	.	S 817	1702	71	.	S 809
1101	71	.	D 690	2105	71	.	S 817	1703	71	.	S 809
1303	71	.	D 698					1705	71	.	S 809
1205	78	.	D 712	IV M 1.8				1601	71	.	S 814
1405	70	.	D 723	ID	AFP	T	D AAD	1602	71	.	S 814
1501	71	.	D 736					1604	71	.	S 814
1105	71	.	D 771	1004	71	.	D 540	1901	70	.	S 822
1302	71	.	D 796	0704	78	.	D 591	1902	70	.	S 822
1204	78	.	D 809	0902	70	.	D 616	1904	70	.	S 822
1401	70	.	D 805	1001	71	.	S 731	1803	71	.	S 827
1102	71	.	S 809	1002	71	.	S 731	1804	71	.	S 827
1103	71	.	S 809	1003	71	.	S 731				
1104	71	.	S 809	1005	71	.	S 731	IV M 0.45			
1202	78	.	S 816	0901	70	.	D 732	ID	AFP	T	D AAD
1203	78	.	S 816	0703	78	.	D 745				
1301	71	.	D 810	0903	70	.	S 744	2805	71	.	D 549
1502	71	.	S 816	0904	70	.	S 744	2905	71	.	D 585
1504	71	.	S 816	0905	70	.	S 744	2802	71	.	D 610
1304	71	.	S 827	0805	71	.	S 752	2604	78	.	D 723
1402	70	.	S 830	0601	71	.	D 757	2705	71	.	D 768
1403	70	.	S 830	0801	71	.	S 758	3004	71	.	D 771
1404	70	.	S 830	0802	71	.	S 758	2701	71	.	D 782
				0803	71	.	S 758	2601	78	.	S 813
IV F 0.45				0804	71	.	S 758	2602	78	.	S 813
ID	AFP	T	D AAD	0701	78	.	D 765	2603	78	.	S 813
				0702	78	.	S 766	2605	78	.	S 813
2304	71	.	D 529	0705	78	.	S 766	2703	71	.	D 807
2205	71	.	D 533	0602	71	.	S 772	2702	71	.	S 814
2203	71	.	D 592	0603	71	.	S 772	2704	71	.	S 814
2204	71	.	D 743	0604	71	.	S 772	2801	71	.	S 814
2505	71	.	D 771	0605	71	.	S 772	2803	71	.	S 814
2102	71	.	D 778					2804	71	.	S 814
2305	71	.	D 778	IV M 0.9				2901	71	.	S 820
2201	71	.	S 806	ID	AFP	T	D AAD	2902	71	.	S 820
2202	71	.	S 806					2903	71	.	S 820
2301	71	.	S 807	1805	71	.	D 477	2904	71	.	S 820
2302	71	.	S 807	1605	71	.	D 613	3001	71	.	S 821
2303	71	.	S 807	1903	70	.	D 672	3002	71	.	S 821
2401	71	.	S 807	1704	71	.	D 701	3003	71	.	S 821
2402	71	.	S 807	1603	71	.	D 725	3005	71	.	S 821
2403	71	.	S 807	1801	71	.	D 726				
2404	71	.	S 807	1905	70	.	D 737				
2405	71	.	S 807	1802	71	.	D 771				

V	F	3.75												
ID	AFP	T	D	AAD	1205	71	679	S	806	0702	71	504	D	767
					1303	70	.	D	758	0703	71	504	S	809
					1504	71	700	S	816	0705	71	504	S	809
0305	71	.	D	288	1104	71	716	S	808	1005	71	529	S	803
0401	71	.	D	369	1301	70	718	S	821	0901	71	550	S	816
0504	71	.	D	495	1302	70	718	S	821	0905	71	550	S	816
0103	71	.	D	523	1305	70	718	S	821	0603	71	552	D	694
0403	71	.	D	558	1502	71	.	D	813	0803	78	557	D	661
0303	71	507	D	698						0801	78	581	D	788
0104	71	518	D	677	V	F	0.94			0802	78	581	D	792
0304	71	550	D	710	ID	AFP	T	D	AAD	1001	71	588	S	803
0205	71	.	D	625						0704	71	595	S	809
0101	71	571	D	743	2302	70	.	D	527	1002	71	609	D	736
0302	71	574	D	760	2402	71	493	S	815	0902	71	609	S	816
0201	71	581	S	815	2105	71	528	S	807	1003	71	.	D	691
0105	71	584	D	659	2502	70	.	D	619	0601	71	651	S	809
0301	71	588	D	760	2202	71	570	S	806	1004	71	721	S	803
0203	71	597	D	717	2103	71	595	S	807					
0502	71	602	S	738	2503	70	.	D	693	V	M	1.87		
0503	71	602	S	738	2504	70	623	S	821	ID	AFP	T	D	AAD
0405	71	.	D	675	2501	70	637	D	801					
0102	71	609	D	780	2205	71	651	S	806	1903	71	336	D	563
0402	71	616	S	752	2404	71	.	D	724	2003	71	420	S	820
0404	71	630	D	724	2304	70	660	D	759	1703	71	514	S	807
0202	71	630	D	750	2405	71	.	D	736	1602	71	528	D	743
0204	71	630	S	815	2102	71	665	S	807	1705	71	557	D	774
0501	71	.	S	738	2201	71	.	D	745	1704	71	557	S	807
0505	71	.	S	738	2505	70	.	D	745	1802	78	557	S	814
	V	F	1.87		2305	70	681	D	788	1605	71	564	D	792
	ID	AFP	T	AAD	2401	71	693	S	815	1603	71	569	S	807
1404	70	368	S	814	2203	71	700	S	806	1804	78	569	S	814
1304	70	.	D	457	2101	71	.	D	795	1601	71	571	S	807
1203	71	.	D	561	2403	71	.	D	804	1604	71	571	S	807
1102	71	.	D	568	2204	71	.	S	806	1701	71	581	S	807
1201	71	534	D	764	2104	71	.	S	807	1805	78	581	S	814
1204	71	540	D	724	2301	70	.	S	821	1801	78	616	S	814
1403	70	543	D	696	2303	70	.	S	821	1803	78	616	S	814
1503	71	571	S	816						2001	71	616	S	820
1101	71	583	D	738	V	M	3.75			2002	71	616	S	820
1401	70	602	D	695	ID	AFP	T	D	AAD	2005	71	616	S	820
1202	71	616	D	736	0604	71	399	D	744	1904	71	630	D	736
1405	70	623	S	814	0701	71	422	D	802	1901	71	644	S	806
1501	71	639	S	816	0903	71	424	D	725	1902	71	644	S	806
1105	71	.	D	715	0804	78	431	D	772	1905	71	.	D	716
1505	71	644	D	793	0605	71	462	D	759	2004	71	.	D	779
1103	71	.	D	717	0805	78	483	D	792	1702	71	.	S	807
1402	70	665	D	752	0904	71	497	D	802					
					0602	71	497	S	809					

V	M	0.94	ID	AFP	T	D	AAD	0102	71	.	S	814	2201	71	.	D	768
								0103	71	.	S	814	2102	71	.	D	792
								0104	71	.	S	814	2403	71	.	D	794
3003	71	324	D	766				0105	71	.	S	814	2105	71	.	D	796
2901	71	380	D	696				0403	71	.	S	821	2103	71	.	S	803
3005	71	.	D	575				0301	71	.	S	823	2202	71	.	S	803
2802	78	.	D	617				0302	71	.	S	823	2204	71	.	S	803
2703	71	550	D	747				0304	71	.	S	823	2205	71	.	S	803
2604	71	564	D	682									2301	71	.	S	806
2701	71	570	D	652									2302	71	.	S	806
3001	71	.	D	648									2303	71	.	S	806
2801	78	.	D	655									2304	71	.	S	806
2702	71	595	S	806				1404	71	406	D	704	2502	71	.	S	807
2605	71	595	S	807				1204	78	.	D	593	2503	71	.	S	807
2602	71	.	D	684				1505	71	.	D	593	2505	71	.	S	807
2803	78	616	D	764				1305	71	.	D	645	2401	71	.	S	809
2704	71	616	S	806				1205	78	.	D	673	2404	71	.	S	809
2705	71	616	S	806				1103	71	.	D	684					
2805	78	616	S	813				1104	71	.	D	701					
2603	71	630	S	807				1405	71	.	D	729					
2904	71	644	S	806				1503	71	.	D	729					
3004	71	.	D	745				1303	71	669	S	806	0901	70	.	D	560
2601	71	693	S	807				1101	71	.	D	743	0902	70	518	D	626
2804	78	714	S	813				1402	71	.	D	743	1002	71	597	S	803
3002	71	.	S	803				1304	71	.	D	764	0602	71	.	D	708
2902	71	.	S	806				1401	71	.	D	766	0703	71	637	S	809
2903	71	.	S	806				1502	71	.	D	772	0905	70	637	S	815
2905	71	.	S	806				1105	71	.	D	775	1004	71	651	S	803
								1203	78	.	D	782	0801	71	.	D	767
VI	F	3.75						1403	71	.	D	797	1001	71	714	S	803
			ID	AFP	T	D	AAD	1301	71	.	D	802	0803	71	729	S	823
								1102	71	.	S	803	0805	71	729	S	823
0405	71	.	D	652				1302	71	.	S	806	0604	71	.	D	802
0503	71	.	D	677				1201	78	.	S	813	1003	71	.	S	803
0303	71	.	D	689				1202	78	.	S	813	1005	71	.	S	803
0401	71	630	S	821				1501	71	.	S	807	0601	71	.	S	809
0305	71	.	D	702				1504	71	.	S	807	0603	71	.	S	809
0402	71	.	D	717									0605	71	.	S	809
0101	71	.	D	757									0701	71	.	S	809
0404	71	.	D	757				VI	F	0.94			0702	71	.	S	809
								ID	AFP	T	D	AAD					
0204	78	.	D	764									0704	71	.	S	809
0505	71	.	D	764				2402	71	.	D	533	0705	71	.	S	809
0502	71	.	D	800				2104	71	.	D	632	0903	70	.	S	815
0501	71	.	S	807				2305	71	.	D	659	0904	70	.	S	815
0504	71	.	S	807				2504	71	.	D	668	0804	71	751	S	823
0201	78	.	S	816				2203	71	.	D	696	0802	71	.	S	823
0202	78	.	S	816				2501	71	.	D	736					
0203	78	.	S	816				2405	71	.	D	746					
0205	78	.	S	816				2101	71	.	D	766					

VI M 1.87				2805 71 . S 808				0903 63 . S 800			
ID	AFP	T	D AAD	2901	70	. S 815	0904	63	. S 800		
1605	71	.	D 649	2902	70	. S 815	1003	63	. S 800		
1503	71	.	D 652	2903	70	. S 815				VII F 15	
1702	71	584	S 807	2905	70	. S 815				ID AFP T D AAD	
2004	71	616	D 736	3002	71	. S 816					
2003	71	616	D 789	3003	71	. S 816					
1901	70	637	D 758	3005	71	. S 816	0201	70	. D 102		
1903	70	.	D 721				0902	63	. D 319		
1604	71	.	D 775	VII F 75			0504	66	. S 441		
1601	71	.	S 803	ID AFP T D AAD			0202	70	. D 513		
1602	71	.	S 803	1001	63	. D 168	1404	60	. D 545		
1902	70	.	D 805	1005	63	. D 504	0604	66	. D 556		
1801	71	.	S 806	1402	61	. D 603	0605	66	. D 616		
1802	71	.	S 806	1303	61	. D 611	1405	60	. D 665		
1803	71	.	S 806	0605	70	. D 641	0102	70	. D 676		
1804	71	.	S 806	0205	70	. D 646	0203	70	. D 707		
1805	71	.	S 806	0601	70	. D 647	1403	60	. D 699		
1701	71	.	S 807	0902	63	. D 687	1003	63	. D 725		
1703	71	.	S 807	1404	61	. D 687	0601	66	. D 732		
1704	71	.	S 807	0204	70	. D 702	0205	70	. D 750		
1705	71	.	S 807	0101	70	. S 703	1304	60	. D 746		
1904	70	.	S 815	0905	63	. D 697	1004	63	. D 749		
1905	70	.	S 815	1401	61	. D 712	0101	70	. D 770		
2001	71	.	S 816	0602	70	. D 723	1001	63	. D 772		
2002	71	.	S 816	0502	70	. D 724	0501	66	. S 775		
2005	71	.	S 816	0901	63	. D 721	0903	63	. D 778		
				0105	70	. D 728	1002	63	. D 795		
				0201	70	. D 735	0502	66	. S 801		
VI M 0.94	ID	AFP	T D AAD	0102	70	. D 739	0503	66	. S 801		
				1304	61	. D 737	0505	66	. D 801		
2705	71	.	D 442	0604	70	689 S 805	0602	66	. S 801		
2801	71	.	D 491	1301	61	. D 754	0603	66	. S 801		
3001	71	.	D 645	0203	70	693 S 805	0103	70	. S 805		
2601	71	.	D 722	1305	61	. D 768	0104	70	. S 805		
3004	71	.	D 730	1002	63	. D 770	0105	70	. S 805		
2904	70	.	D 795	1004	63	. D 779	0204	70	. S 805		
2701	71	.	S 806	1403	61	. D 782	1301	60	. S 797		
2702	71	.	S 806	1302	61	. S 796	1302	60	. S 797		
2703	71	.	S 806	1405	61	. S 796	1303	60	. S 797		
2704	71	.	S 806	0103	70	735 S 805	1305	60	. S 797		
2602	71	.	S 807	0104	70	. S 805	1401	60	. S 797		
2603	71	.	S 807	0202	70	. S 805	1402	60	. S 797		
2604	71	.	S 807	0501	70	. S 805	0901	63	. S 800		
2605	71	.	S 807	0503	70	. S 805	0904	63	. S 800		
2802	71	.	S 808	0504	70	. S 805	0905	63	. S 800		
2803	71	.	S 808	0505	70	. S 805	1005	63	. S 801		
2804	71	.	S 808	0603	70	. S 805					

VII	M	75	1104	63	. D	539	0201	76	. D	709		
ID	AFP	T	D	AAD	0803	69	. D	610	0505	71	. D	719
1603	60	.	D	222	1201	63	. D	693	0403	71	. D	723
0805	70	.	D	408	0704	69	. D	701	0404	71	. D	729
0704	70	.	D	449	1604	59	. D	713	0502	71	. D	736
1204	53	.	D	544	1505	59	. D	706	0503	71	. D	748
1104	64	.	D	610	1605	59	. D	714	0102	69	. D	755
1105	64	.	D	654	1603	59	. D	731	0101	69	. D	764
0403	72	.	D	675	1203	63	. D	735	0202	76	. S	766
0305	72	.	D	702	1503	59	. D	742	0302	71	. S	766
1502	60	.	D	719	1105	63	. D	747	0303	71	. S	766
0301	72	672	S	807	1601	59	. D	756	0305	71	. S	766
1203	53	.	D	739	0702	69	. D	759	0501	71	. D	766
1503	60	.	D	762	0701	69	. S	794	0104	69	. D	784
0702	70	.	D	785	0703	69	. S	804	0504	71	. D	793
0703	70	.	D	793	0705	69	. S	804	0204	76	. S	799
0701	70	.	D	794	0801	69	. S	804	0105	69	. S	799
0803	70	.	D	798	0802	69	. S	804	0402	71	. S	809
0405	72	.	D	804	0804	69	. S	804	VIII	F	4.5	
1501	60	.	D	794	0301	70	. S	805	ID	AFP	T	D AAD
1505	60	.	D	794	0302	70	. S	805	1503	71	. D	387
1504	60	.	S	795	0303	70	. S	805	1404	70	. D	723
0705	70	.	S	805	0304	70	. S	805	1502	71	. D	724
0801	70	.	S	805	0305	70	. S	805	1303	71	. D	738
0802	70	.	S	805	0401	70	. S	805	1401	70	. D	738
0804	70	.	S	805	0402	70	. S	805	1105	66	. D	735
0302	72	735	S	807	0403	70	. S	805	1101	66	. D	739
0303	72	.	S	807	0405	70	. S	805	1203	71	. D	750
0304	72	.	S	807	1501	59	. S	796	1405	70	. D	751
0401	72	.	S	807	1502	59	. S	796	1304	71	. D	760
0402	72	.	S	807	1504	59	. S	796	1403	70	. D	767
0404	72	.	S	807	1602	59	. S	796	1201	71	. S	800
1601	60	.	S	796	1101	63	. S	801	1202	71	. S	800
1602	60	.	S	796	1102	63	. S	801	1204	71	. S	800
1604	60	.	S	796	1103	63	. S	801	1205	71	. S	800
1605	60	.	S	796	1202	63	. S	801	1102	66	. S	801
1201	53	.	S	790	1205	63	. S	801	1103	66	. S	801
1202	53	.	S	790	VIII	F	9	1104	66	. S	801	
1205	53	.	S	790	ID	AFP	T	1501	71	. S	806	
1101	64	.	S	801	0401	71	. D	366	1504	71	. S	806
1102	64	.	S	801	0405	71	. D	491	0301	71	. S	808
1103	64	.	S	801	0205	76	. D	556	1302	71	. S	808
VII	M	15	0103	69	0304	71	. D	587	1305	71	. S	808
ID	AFP	T	D	AAD	0405	71	. D	659	1402	70	. S	809
0805	69	.	D	479	0203	76	. D	673				
1204	63	.	D	522				0203				

VIII	F	2.25	ID	AFP	T	D AAD	0602	73	. S	809	3004	71	. S	803
2404	71	. D	264				0701	71	. S	809	3005	71	. S	803
2503	71	. D	499				0704	71	. S	809	2602	70	. S	805
2105	66	. D	622				0904	70	. S	809	2604	70	. S	805
2401	71	. D	732				0905	70	. S	809	2701	71	. S	806
2405	71	. D	750				0801	71	. S	814	2702	71	. S	806
2103	66	. D	759				0802	71	. S	814	2703	71	. S	806
2504	71	. D	782				0803	71	. S	814	2704	71	. S	806
2203	76	. D	794								2705	71	. S	806
2505	71	. D	799								2901	70	. S	809
2102	66	. D	796								2902	70	. S	809
2101	66	. S	801								2904	70	. S	809
2104	66	. S	801								2905	70	. S	809
2501	71	. S	806								2901	71	. S	814
2502	71	. S	806								2802	71	. S	814
2201	76	. S	811								2803	71	. S	814
2202	76	. S	811								2805	71	. S	814
2204	76	. S	811											
2205	76	. S	811											
2402	71	. S	808											
2403	71	. S	808											
2301	71	. S	809											
2302	71	. S	809											
2303	71	. S	809											
2304	71	. S	809											
2305	71	. S	809											
VIII	M	9	ID	AFP	T	D AAD	1801	78	. D	515	0203	71	. D	431
							1902	70	. D	700	0303	71	. D	659
							2003	71	. D	703	0505	71	. D	673
							1703	69	. D	709	0104	71	. D	746
							1701	69	. D	778	0504	71	. D	765
							1802	78	. S	807	0103	71	. D	766
							1803	78	. S	807	0502	71	. D	794
							1804	78	. S	807	0201	71	. D	799
							1805	78	. S	807	0202	71	. S	802
							2001	71	. S	802	0204	71	. S	802
							2002	71	. S	802	0205	71	. S	802
							2004	71	. S	802	0501	71	. S	803
							2005	71	. S	802	0503	71	. S	803
							1601	70	. S	802	0401	71	. S	806
							1602	70	. S	802	0402	71	. S	806
							1603	70	. S	802	0403	71	. S	806
							1604	70	. S	802	0404	71	. S	806
							1605	70	. S	802	0202	71	. S	802
							1904	70	. D	806	0204	71	. S	802
							1702	69	. S	806	0205	71	. S	802
							1704	69	. S	806	0501	71	. S	803
							1705	69	. S	806	0503	71	. S	803
							1901	70	. S	807	0401	71	. S	806
							1903	70	. S	807	0402	71	. S	806
							1905	70	. S	807	0403	71	. S	806
											0404	71	. S	806
											0405	71	. S	806
											0101	71	. S	807
											0102	71	. S	807
											0103	71	. S	807
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											0301	71	. S	807
											0302	71	. S	807
											0304	71	. S	807
											0305	71	. S	807
VIII	M	2.25	ID	AFP	T	D AAD	2601	70	. D	448	0105	71	. S	807
							2605	70	. D	486	0301	71	. S	807
							2903	70	. D	616	0302	71	. S	807
							3003	71	. D	711	0304	71	. S	807
							2603	70	. D	746	0305	71	. S	807
							2804	71	. D	787				
							3002	71	. D	800				
							3001	71	. D	802				

IX F 1.5				2103 71 . S 806				1703 71 . S 802				
ID	AFP	T	D AAD	2104	71	. S 806	1704	71	. S 802	1705	71	
1204	71	.	D 578	2503	71	. S 806	1803	78	. S 809	1804	78	
1501	71	.	D 638	2401	71	. S 807	1805	78	. S 809	1901	71	
1202	71	.	D 649	2402	71	. S 807	1902	71	. S 806	1903	71	
1305	71	.	D 705	2403	71	. S 807	1904	71	. S 806	1905	71	
1101	71	.	D 711	2405	71	. S 807	1906			1605	71	
1403	70	.	D 714				1907			2001	71	
1304	71	.	D 719	IX	M	3	1908			2002	71	
1504	71	.	D 759	ID	AFP	T	D AAD			2003	71	
1103	71	.	D 766	0601	71	. D 614	1606			2004	71	
1405	70	.	D 780	0905	70	. D 665	1607			2005	71	
1201	71	.	S 802	0703	71	. D 683	1608			2006	71	
1203	71	.	S 802	0902	70	. D 746	1609			2007	71	
1205	71	.	S 802	0901	70	. S 805	1610			2008	71	
1401	70	.	S 805	0903	70	. S 805	1611			2009	71	
1402	70	.	S 805	0904	70	. S 805	1612			2010	71	
1404	70	.	S 805	1001	71	. S 806	1613			2011	71	
1102	71	.	S 806	1002	71	. S 806	1614			2012	71	
1104	71	.	S 806	1003	71	. S 806	1615			2013	71	
1105	71	.	S 806	1004	71	. S 806	1616			2014	71	
1502	71	.	S 808	1005	71	. S 806	1617			2015	71	
1503	71	.	S 808	0602	71	. S 807	1618			2016	71	
1505	71	.	S 808	0603	71	. S 807	1619			2017	71	
1301	71	.	S 809	0604	71	. S 807	1620			2018	71	
1302	71	.	S 809	0605	71	. S 807	1621			2019	71	
1303	71	.	S 809	0701	71	. S 807	1622			2020	71	
				0702	71	. S 807	1623			2021	71	
				0704	71	. S 807	1624			2022	71	
				0705	71	. S 807	1625			2023	71	
2501	71	.	D 625	0801	71	. S 809	2703	78	. S 809	2704	78	
2502	71	.	D 634	0802	71	. S 809	2705	78	. S 809	2706	78	
2302	71	.	D 696	0803	71	. S 809	2707	78	. S 809	2708	78	
2304	71	.	D 705	0804	71	. S 809	2709	78	. S 809	2710	78	
2201	71	.	D 708	0805	71	. S 809	2711	78	. S 809	2712	78	
2505	71	.	D 726				2713	78	. S 809	2714	78	
2102	71	.	D 729	IX	M	1.5	2715	78	. S 809	2716	78	
2105	71	.	D 729	ID	AFP	T	D AAD	2717	78	. S 809	2718	78
2101	71	.	D 740	0806	71	. S 809	2719	78	. S 809	2720	78	
2404	71	.	D 785	1604	71	. D 589	2901	71	. S 808	2902	71	
2202	71	.	S 802	1802	78	. D 596	2903	71	. S 808	2904	71	
2203	71	.	S 802	2005	71	. D 607	2905	71	. S 808	2906	71	
2204	71	.	S 802	1602	71	. D 715	2907	71	. S 808	2908	71	
2205	71	.	S 802	2004	71	. D 736	2909	71	. S 808	2910	71	
2301	71	.	S 802	1801	78	. D 796						
2303	71	.	S 802	1701	71	. S 802						
2305	71	.	S 802	1702	71	. S 802						

X	F	0.015		X	F	0.0075		1104	70	595	S	681		
ID	APP	T	D	AAD	ID	APP	T	D	AAD					
0203	70	227	S	490	1305	70	317	D	513					
0105	70	231	D	361	1303	71	.	D	396	1301	71	.	D	677
0204	70	252	S	490	1404	71	340	D	662	1501	71	.	S	683
0205	70	262	S	490	1204	70	364	D	560	1103	70	.	S	694
0203	70	266	D	438	1105	70	380	D	662					
0402	71	275	S	479	1203	70	400	D	590	2501	71	.	D	334
0501	71	281	S	463	1201	70	400	D	595	2501	71	.	D	424
0401	71	283	S	479	1301	70	406	D	637	2403	71	480	D	666
0303	70	289	S	492	1205	70	417	D	570	2303	70	.	D	560
0304	70	289	S	492	1303	70	417	D	625	2301	70	.	D	562
0405	71	290	D	100	1502	71	421	D	631	2405	71	.	D	584
0202	70	297	D	455	1304	71	428	D	606	2304	70	532	D	665
0102	70	297	S	490	1503	71	434	D	600	2303	71	555	D	667
0104	70	297	S	490	1304	70	434	D	638	2503	71	.	D	631
0105	70	297	S	490	1202	70	434	D	641	2203	70	.	D	648
0201	70	297	S	492	1403	71	444	D	649	2105	70	581	D	681
0401	71	304	D	456	1505	71	455	S	682	2402	71	.	D	668
0402	71	304	S	470	1201	70	462	D	606	2404	71	602	S	807
0403	71	304	S	470	1105	70	462	D	665	2101	70	.	D	716
0404	71	304	S	470	1205	70	469	S	694	2302	70	.	D	723
0201	70	309	D	479	1405	71	470	D	635	2401	71	.	D	726
0103	70	309	S	490	1102	70	470	D	648	2202	70	660	D	772
0204	70	315	D	483	1504	71	473	D	634	2201	70	660	S	834
0505	71	323	S	463	1502	71	473	D	676	2204	70	660	S	834
0101	70	325	S	490	1203	70	476	D	690	2505	71	665	D	794
0102	70	329	D	490	1505	71	477	D	674	2305	70	.	D	742
0101	70	329	S	492	1504	71	477	S	683	2502	71	679	S	814
0104	70	329	S	492	1402	71	.	D	554	2201	70	688	S	820
0404	71	332	S	479	1102	70	483	D	626	2204	70	.	D	763
0405	71	332	S	479	1405	71	487	D	641	2504	71	707	D	794
0305	70	336	S	492	1503	71	490	D	673	2103	70	721	S	834
0501	71	340	S	466	1501	71	490	S	682	2304	71	721	S	837
0504	71	340	S	466	1202	70	497	S	697	2104	70	728	S	820
0505	71	343	S	466	1402	71	518	S	684	2105	70	728	S	834
0103	70	346	D	490	1204	70	532	S	697	2301	71	.	D	801
0503	71	354	S	463	1401	71	539	D	676	2401	71	.	D	801
0403	71	357	S	479	1401	71	546	D	652	2402	71	.	S	807
0503	71	361	S	466	1404	71	549	S	684	2502	71	.	S	813
0301	70	368	S	492	1302	70	556	D	630	2504	71	.	S	813
0502	71	372	S	463	1403	71	560	S	683	2503	71	.	S	814
0205	70	379	S	492	1104	70	567	S	694	2505	71	.	S	814
0302	70	379	S	492	1101	70	571	S	681	2102	70	.	S	820
0504	71	382	S	463	1305	71	571	S	691	2202	70	.	S	820
0502	71	.	S	466	1103	70	581	S	681	2205	70	.	S	820
0202	70	395	S	492	1101	70	588	S	694	2403	71	.	S	821
					1302	71	589	D	680	2404	71	.	S	821

2405	71	.	S	821	3402	71	.	S	822	0704	70	329	S	493
2203	70	.	D	821	3403	71	.	S	822	0902	71	332	S	481
2103	70	.	S	821	3102	70	.	D	822	0603	70	337	S	491
2101	70	.	S	834	3101	70	.	D	826	0604	70	337	S	491
2102	70	.	S	834	3104	70	.	S	826	0805	70	337	S	492
2104	70	.	S	834	3105	70	.	S	826	0803	71	339	S	488
2205	70	.	S	834	3203	70	.	S	840	1001	71	340	S	472
2302	71	.	S	837	3201	70	.	S	840	1003	71	340	S	472
2305	71	.	S	837	3204	70	.	S	840	0701	70	346	S	493
					3103	70	.	S	844	0804	71	352	S	488
X	F	.	001875		3104	70	.	S	844	0903	71	359	S	485
ID	AFP	T	D	AAD	3302	70	.	S	844	0803	70	359	S	492
					3303	70	.	S	844	1004	71	361	S	472
3503	71	.	D	561	3304	70	.	S	844	1004	71	371	S	474
3301	70	.	D	563						1005	71	371	S	474
3201	70	.	D	569	X	M	0.015			0604	70	389	S	493
3301	71	.	D	575	ID	AFP	T	D	AAD	1002	71	392	S	474
3405	71	.	D	592						1003	71	.	S	474
3204	70	.	D	592	0702	70	214	S	491	0703	70	408	S	491
3502	71	.	D	669	0905	71	218	S	485					
3205	70	.	D	673	0703	70	227	S	493	X	M	0.0075		
3403	71	613	D	715	0904	71	239	S	485	ID	AFP	T	D	AAD
3101	70	.	D	692	0605	70	.	S	316	1703	70	323	D	630
3402	71	.	D	696	0704	70	246	D	438	1601	70	331	D	583
3102	70	.	D	709	0904	71	246	S	481	1704	70	351	D	654
3103	70	.	D	714	0802	71	252	D	436	1705	70	351	S	694
3504	71	644	S	815	0903	71	254	D	435	1904	71	359	D	442
3205	70	.	D	721	0603	70	259	S	493	1603	70	359	D	522
3302	71	.	D	726	0605	70	260	D	436	2005	71	371	D	519
3404	71	.	D	737	1005	71	276	S	472	1604	70	375	D	541
3202	70	.	D	738	0701	70	276	S	491	1901	71	375	D	561
3501	71	.	D	766	0702	70	289	D	392	1903	71	375	D	631
3303	71	.	D	778	0901	71	290	D	430	1803	70	395	S	682
3202	70	.	D	784	0805	71	291	S	488	2002	71	413	D	493
3401	71	.	D	785	0801	71	294	S	488	1604	70	413	S	694
3305	70	.	D	787	0802	70	297	D	485	1802	71	420	S	691
3203	70	.	D	794	0602	70	297	S	491	1801	71	421	D	673
3105	70	.	D	798	0804	70	297	S	492	1701	70	427	D	673
3505	71	.	D	801	0901	71	301	S	481	1804	70	427	S	682
3404	71	.	S	807	0905	71	301	S	481	2004	71	428	D	659
3405	71	.	S	807	0902	71	302	S	485	1605	70	435	S	694
3502	71	.	S	807	1001	71	308	S	474	1802	70	436	S	682
3504	71	.	S	807	0601	70	309	S	491	2003	71	441	S	683
3505	71	.	S	807	0705	70	309	S	491	1803	71	455	S	691
3304	71	.	D	809	0801	70	309	S	492	1901	71	462	S	684
3501	71	.	S	815	0602	70	315	S	493	1702	70	462	S	694
3503	71	.	S	815	0705	70	315	S	493					
3305	71	.	S	816	1002	71	316	S	472					
3401	71	.	S	822	0601	70	329	S	493					

1905	71	469	S	684	2802	70	.	D	752	3905	71	.	D	809
1601	70	487	S	694	2901	71	686	S	836	3601	70	.	D	815
1602	70	487	S	694	3001	71	700	S	807	3603	70	.	S	816
1701	70	490	S	686	3002	71	700	S	807	3604	70	.	S	816
1704	70	490	S	686	2703	70	700	S	808	3605	70	.	S	816
1902	71	498	S	691	2704	70	700	S	820	4001	71	.	S	822
1905	71	498	S	691	2602	70	707	S	834	4004	71	.	S	822
1801	70	501	S	682	3004	71	.	D	790	4005	71	.	S	822
1805	70	501	S	682	2603	70	721	S	820	3604	70	.	D	822
1903	71	504	S	684	2603	70	721	S	834	3803	71	752	S	823
1603	70	505	S	694	3005	71	.	S	807	3805	71	.	S	823
2004	71	511	S	683	2701	70	.	S	808	3901	71	.	S	827
1904	71	518	S	684	2803	70	742	S	843	3902	71	.	S	827
1705	70	518	S	686	2604	70	.	D	813	3903	71	.	S	827
1804	71	528	S	691	2705	70	.	S	820	3901	71	.	S	830
1602	70	532	D	669	2604	70	.	D	821	3902	71	.	S	830
1703	70	532	S	686	3001	71	.	S	823	3903	71	.	S	830
2001	71	542	S	683	3002	71	.	S	823	3904	71	.	S	830
2005	71	546	S	683	3003	71	.	S	823	3905	71	.	S	830
2003	71	560	S	683	3005	71	.	S	823	3602	70	.	S	842
1902	71	567	S	684	2601	70	.	D	826	3603	70	.	S	842
2001	71	571	S	683	2805	71	.	S	828	3605	70	.	S	842
1702	70	581	S	686	2902	71	.	S	836	3701	70	.	S	844
1805	71	581	S	691	2801	70	.	S	843	3703	70	.	S	844
										3704	70	.	S	844

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2802	71	373	D	695
2905	71	396	S	836
3003	71	434	D	598
2704	70	535	S	808
2601	70	.	D	610
2703	70	.	D	623
2903	71	555	D	743
2702	70	567	D	801
2805	70	.	D	639
2903	71	581	S	828
2605	70	623	D	801
2904	71	630	D	773
2804	70	634	S	843
2701	70	637	S	820
2605	70	.	D	711
3004	71	644	S	807
2804	71	653	D	743
2801	71	653	S	828
2602	70	667	S	821
2705	70	672	S	808
2702	70	679	S	820

X M .001875  
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3601	70	.	D	388
4003	71	.	D	577
3702	70	.	D	610
3801	70	.	D	618
3703	70	.	D	683
3704	70	.	D	707
3804	71	.	D	736
3602	70	.	D	739
3802	71	.	D	743
3802	70	.	D	760
4002	71	.	D	792
3904	71	.	D	792
3801	71	721	S	823
3701	70	.	S	805
3702	70	.	S	805
3705	70	.	S	805
4003	71	.	D	806
4001	71	.	S	807
4002	71	.	S	807
4004	71	.	S	807
4005	71	.	S	807

XI F 0.15  
ID AFP T D AAD

1301	67	96	S	226
0601	60	106	S	211
0602	60	106	S	211
0902	63	111	S	218
1002	63	111	S	218
1003	63	111	S	218
1005	63	111	S	218
0502	60	113	S	211
1302	67	115	S	226
1304	67	115	S	226
1305	67	115	S	226
1401	67	115	S	226
1402	67	115	S	226
1404	67	115	S	226
1405	67	115	S	226
0104	66	120	S	216

0105	66	120	S	216	0103	65	280	S	375	0803	60	132	S	215
0504	60	122	S	211	0104	65	280	S	375	0805	60	132	S	215
0901	63	126	S	218	0201	65	280	S	375	1102	63	134	S	220
0903	63	126	S	218	0204	65	280	S	375	1104	63	134	S	220
0904	63	126	S	218	0902	63	287	S	373	1203	63	134	S	220
0905	63	126	S	218	0602	58	296	S	368	1503	66	136	S	225
1001	63	126	S	218	1401	67	297	S	379	1604	66	136	S	225
1004	63	126	S	218	1403	67	297	S	379	0303	66	139	S	217
0604	60	128	S	211	1404	67	297	S	379	0304	66	139	S	217
0201	66	129	S	216	0601	58	308	S	368	0405	66	139	S	217
0202	66	129	S	216	0502	58	.	S	368	1204	63	147	S	220
0203	66	129	S	216	0904	63	.	S	373	0705	60	155	S	215
0204	66	129	S	216	1002	63	.	S	373	1602	66	159	S	225
0205	66	129	S	216	1003	63	.	S	373	1603	66	159	S	225
0501	60	132	S	211	1004	63	.	S	373	XI	M	0.015		
0503	60	132	S	211	0102	65	.	S	375	ID	AFP	T	D	AAD
0505	60	132	S	211	1302	67	.	S	379	1202	63	205	S	373
0603	60	132	S	211	1305	67	.	S	379	0304	66	214	S	376
0605	60	132	S	211	1405	67	.	S	379	0305	66	219	S	376
0101	66	135	S	216	XI	M	0.15			1603	60	231	S	372
0102	66	135	S	216	ID	AFP	T	D	AAD	0705	63	231	S	373
0103	66	135	S	216	1303	67	136	S	226	1501	66	100	S	225
					1403	67	136	S	226	0701	60	106	S	215
XI	F	0.015			0801	60	106	S	215	1201	63	246	S	373
ID	AFP	T	D	AAD	0401	66	108	S	217	1204	63	246	S	373
0101	65	175	S	375	0402	66	108	S	217	0302	66	248	S	376
0903	63	220	D	340	1201	63	111	S	220	1604	60	256	S	372
0203	65	226	S	375	0704	60	113	S	215	0703	63	241	S	373
0505	58	231	S	368	0301	66	113	S	217	1204	63	246	S	373
1304	67	231	S	379	0302	66	113	S	217	0302	66	248	S	376
0205	65	238	S	375	0403	66	113	S	217	1604	60	256	S	372
0501	58	241	S	368	0404	66	113	S	217	0701	63	273	S	373
0504	58	241	S	368	1504	66	115	S	225	0704	63	273	S	373
0605	58	241	S	368	1505	66	115	S	225	1101	63	275	S	373
0901	63	246	S	373	1601	66	115	S	225	1501	60	276	S	372
1001	63	252	S	373	1605	66	115	S	225	1502	60	276	S	372
1402	67	256	S	379	0305	66	120	S	217	1503	60	276	S	372
0603	58	263	S	368	0804	60	122	S	215	1504	60	276	S	372
0905	63	267	S	373	1502	66	123	S	225	1505	60	276	S	372
1005	63	267	S	373	1101	63	126	S	220	1102	63	280	S	373
1301	67	269	S	379	1103	63	126	S	220	0402	66	280	S	376
1303	67	269	S	379	1105	63	126	S	220	0404	66	280	S	376
0105	65	270	S	375	1202	63	126	S	220	1105	63	287	S	373
0503	58	273	S	368	1205	63	126	S	220	0803	64	288	S	374
0604	58	273	S	368	0702	60	132	S	215	0804	64	288	S	374
0202	65	274	S	375	0703	60	132	S	215	0301	66	291	S	376
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	ID	AFP	T	D	AAD		
1601	70	.	S 802	0405	71 560 D 754		
1801	71	.	S 803	0301	71 574 D 757		
1802	71	.	S 803	0304	71 574 S 814		
1803	71	.	S 803	0303	71 575 D 654	2204 71 . D 375	
1804	71	.	S 803	0203	71 581 D 732	2502 71 448 D 688	
1901	70	.	S 805	0201	71 582 S 814	2102 71 . D 547	
1903	70	.	S 805	0305	71 609 S 814	2501 71 567 D 661	
2001	71	.	S 806	0503	71 616 D 797	2301 71 574 D 710	
				0205	71 616 S 814	2303 71 585 D 757	
A	M	18.75		0104	71 620 D 795	2105 71 595 S 802	
	ID	AFP	T	D AAD	0404	71 630 S 802	2203 71 616 D 760
					0204	71 640 D 743	2103 71 630 D 704
2904	70	.	D 500	0202	71 . D 715	2302 71 633 D 782	
2801	78	.	D 561	0505	71 . D 715	2504 71 . D 708	
2701	71	.	D 571	0105	71 . D 729	2205 71 640 S 803	
2705	71	504	D 775	0101	71 665 D 779	2505 71 658 S 806	
2704	71	522	D 687	0402	71 . S 802	2401 70 665 S 805	
3001	71	542	D 708			2402 70 665 S 805	
3003	71	564	D 808	B	F 1.87	2404 70 665 S 805	
3005	71	.	D 638	ID	AFP T D AAD	2503 71 . D 768	
3002	71	.	D 647			2403 70 707 S 805	
2602	73	598	S 808	1201	71 336 D 556	2405 70 707 S 805	
2603	73	598	S 808	1203	71 400 D 673	2305 71 . D 782	
2803	78	640	S 807	1202	71 . D 498	2304 71 714 S 806	
2604	73	651	S 808	1303	78 . D 522	2201 71 . D 793	
2703	71	661	S 803	1403	71 473 S 803	2101 71 . D 799	
2805	78	.	D 747	1405	71 542 D 764	2104 71 . S 802	
2802	78	.	D 764	1404	71 542 S 803	2202 71 . S 803	
3004	71	.	D 758	1204	71 563 D 778		
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2702	71	.	S 803	1502	71 574 D 771		
2901	70	.	S 805	1505	71 574 D 817	0701 78 . S 109	
2902	70	.	D 805	1401	71 581 S 774	0905 71 366 D 558	
2903	70	.	S 805	1301	78 581 S 814	0604 71 407 S 809	
2601	73	.	S 808	1103	71 595 S 802	0603 71 444 S 809	
2605	73	.	S 808	1104	71 595 S 802	0705 78 463 D 796	
				1102	71 . D 676	0901 71 491 D 661	
B	F	3.75		1501	71 . D 679	0903 71 491 D 704	
	ID	AFP	T	D AAD	1504	71 612 S 817	0803 71 491 D 710
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0401	71	409	S 802	1305	78 616 S 814	0602 71 512 D 773	
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0103	71	512	D 773	1503	71 665 S 817	1005 71 553 S 827	
0501	71	514	D 778			0805 71 556 S 814	
0403	71	.	D 620			0702 78 563 S 821	
0102	71	550	S 809			0904 71 570 D 716	

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0802	71	574	S	814	2805	71	.	D 645	
0704	78	581	D	745	2604	71	577	S 802	
0703	78	581	S	821	2605	71	577	S 802	
1004	71	588	S	827	2704	71	581	D 729	
0601	71	.	D	677	2602	71	595	D 793	
1002	71	609	D	708	2601	71	595	S 802	
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	ID	AFP	T	D AAD	2803	71	644	S 809	
					3003	71	651	D 806	
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	1801	71	487	S 806	2701	71	679	S 803	
	1705	71	494	D 682	3001	71	686	D 804	
	1702	71	494	S 807	3005	71	686	S 824	
	1805	71	499	D 775	2702	71	721	S 803	
	2004	71	553	D 794	3002	71	.	S 824	
	2002	71	553	S 817		C	F	75	
	1803	71	556	D 757		ID	AFP	T	D AAD
	1604	71	563	S 802	0501	71	449	D 738	
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	1901	70	588	D 714	0201	71	501	D 726	
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	1603	71	595	S 802	0402	70	.	D 617	
	1903	70	602	D 777	0503	71	.	D 666	
	1902	70	.	D 673	0203	71	623	D 768	
	2001	71	612	S 817	0401	70	.	D 702	
	2003	71	612	S 817	0301	71	.	D 725	
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	1602	71	630	S 802	0303	71	672	S 772	
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	2801	71	.	D 424	0403	70	.	S 809	
	2904	71	.	D 431	0404	70	.	S 809	
	2902	71	438	D 645	0405	70	.	S 809	
	2705	71	483	S 803		C	F	18.75	
	2603	71	532	S 802		ID	AFP	T	D AAD
	2905	71	556	S 806	2403	71	542	D 726	
	2703	71	563	D 761	2402	71	560	S 802	
	2802	71	564	D 750	2302	78	.	D 656	
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					2202	78	679	S 814	
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					2301	78	721	S 807	

2502	71	.	D	793	1605	70	637	S	806	D	F	75							
2503	71	.	S	796	1902	70	637	S	807	ID	AFP	T	D	AAD					
2404	71	.	S	802	1803	71	651	S	800	0203	71	540	D	799					
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2105	70	.	S	802	2002	71	665	S	808	0205	71	585	D	757					
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C	M			75	2001	71	693	S	808	0403	71	.	D	722					
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1002	71	.	D	317	1601	70	736	S	806	1901	70	.	S	807	0303	71	672	S	807
0902	71	.	D	554	2004	71	.	S	808	2005	71	.	S	808	0101	71	695	D	792
0802	71	498	S	779	2004	71	.	S	808	2005	71	.	S	808	0104	71	700	D	803
0901	71	.	D	621	2005	71	.	S	808	C	M	18.75	0202	71	714	S	814		
0803	71	.	D	631						0302	71	.	D	800	0304	71	.	S	807
0903	71	575	D	750						0305	71	.	S	807					
1005	71	588	D	661						0402	71	.	S	807					
0701	69	.	D	678						0102	71	.	S	808					
0603	69	609	D	791						2902	70	.	D	525	0103	71	.	S	808
0702	69	609	S	806						2901	70	484	D	704	0105	71	.	D	808
0904	71	633	S	772						3001	71	490	D	761	0204	71	.	S	814
1003	71	.	S	718						2804	71	518	D	729	0501	71	.	S	820
0805	71	679	S	779						2905	70	549	D	778	0502	71	.	S	820
0703	69	679	S	806						3003	71	553	S	806	0503	71	.	S	820
0804	71	693	S	779						2703	71	595	S	807	0505	71	.	S	820
0705	69	702	S	806						2805	71	616	S	807					
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0601	69	.	S	806						3002	71	.	D	695	ID	AFP	T	D	AAD
0602	69	.	S	806						2705	71	637	S	807	1401	71	.	D	233
0604	69	.	S	806						2802	71	651	S	807	1403	71	.	D	542
0605	69	.	S	806						2803	71	.	D	740	1303	71	.	D	652
0704	69	.	S	806						2704	71	672	S	807	1305	71	.	D	659
1001	71	.	S	809						2801	71	.	D	764	1302	71	.	D	668
1004	71	.	S	809						3005	71	693	S	806	2701	71	700	S	807
0905	71	.	S	822						2601	66	714	S	802	1201	71	616	S	800
C	M			37.5						2603	66	714	S	802	1405	71	.	D	698
	ID	AFP	T	D AAD						2605	66	714	S	802	1104	71	637	S	803
										2702	71	714	S	807	1304	71	.	D	715
1904	70	484	D	774						2602	66	.	S	802	1503	71	651	S	809
1905	70	504	D	749						2604	66	.	S	802	1504	71	.	D	750
1802	71	563	D	771						2903	70	.	S	806	1102	71	.	D	785
2003	71	588	S	808						2904	70	.	S	806	1502	71	.	D	799
1801	71	602	S	800						2904	70	.	S	806	1202	71	.	S	800
1703	71	602	S	806										1203	71	.	S	800	
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1704	71	637	D	792										1205	71	.	S	800	

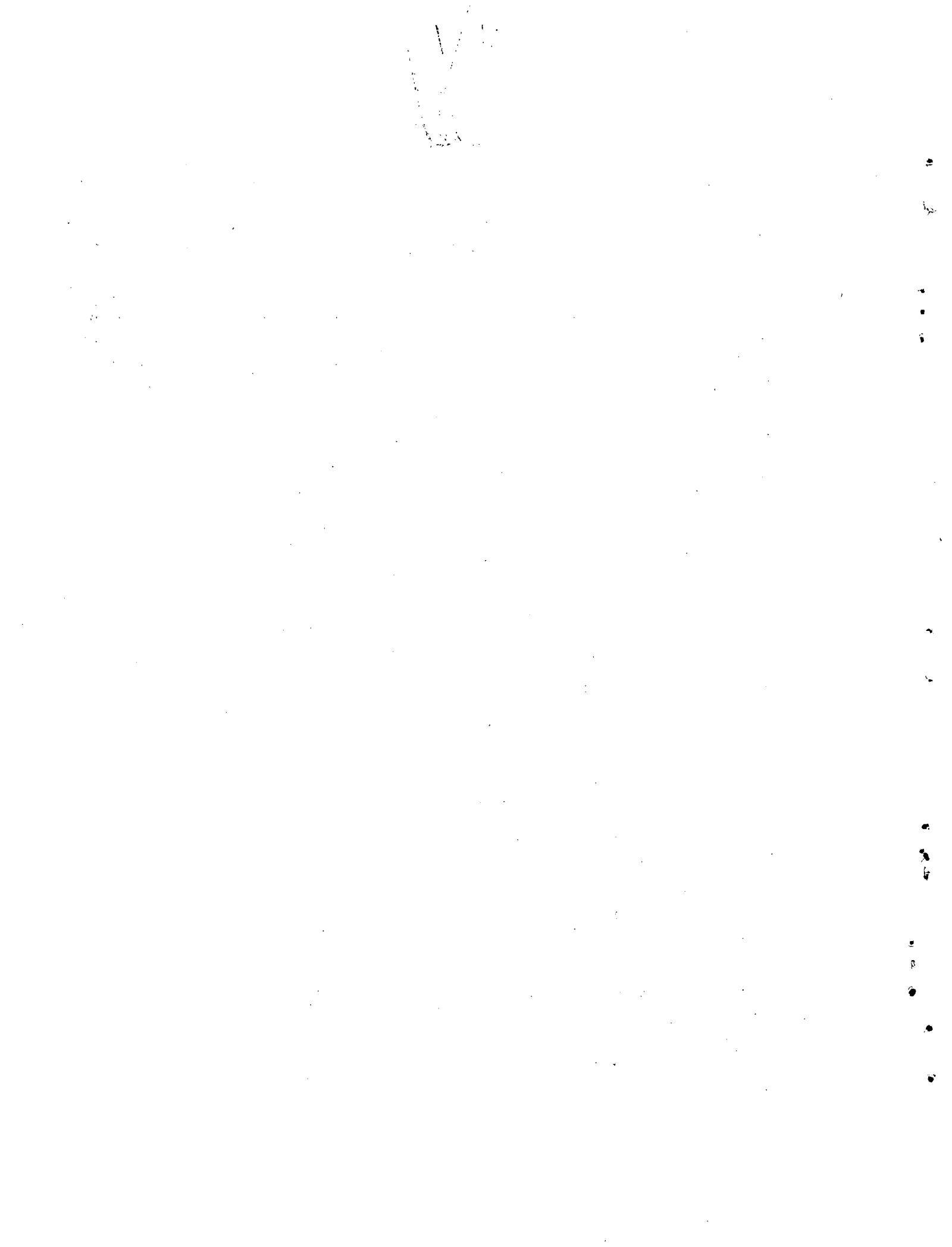
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1103	71	.	S 803
1105	71	.	S 803
1301	71	.	S 806
1404	71	.	S 809
1501	71	.	S 809
1505	71	.	S 809
			0904
D	ID	M	18.75
F	AFP	T	D AAD
0602	71	661	S 807
0605	71	661	S 807
1005	71	665	S 813
0903	71	672	S 808
0805	78	679	S 814
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0603	71	.	S 807
0801	78	.	S 814
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2304	71	.	S 815
2305	71	.	S 815
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F	AFP	T	D AAD
1903	70	.	D 99
1705	71	.	D 212
2005	71	.	D 395
1904	70	.	D 588
1802	78	.	D 619
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1704	71	591	D 757
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1702	71	623	S 806
2001	71	630	S 808
1902	70	.	D 732
1901	70	665	D 795
1801	78	679	S 807
2002	71	.	D 754
1601	71	700	S 808
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1905	70	.	S 805
1602	71	.	S 808
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2003	71	.	S 808
2004	71	.	S 808
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F	AFP	T	D AAD
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0103	70	.	D 555
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0203	70	.	D 587
1305	60	.	D 589
1005	62	.	D 622
0201	70	.	D 655
1405	60	.	D 652
1402	60	.	D 656
1304	60	.	D 669
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0502	66	.	S	802	0104	69	.	S	805	0302	69	.	S	805
0503	66	.	S	802	0105	69	.	S	805	0304	69	.	S	805
0505	66	.	S	802	0202	69	.	S	805	0403	69	.	S	805
0601	66	.	S	802	0901	58	.	S	797	0405	69	.	S	805
0603	66	.	S	802	0902	58	.	S	797	1501	59	.	S	796
0604	66	.	S	802	0903	58	.	S	797	1503	59	.	S	796
0605	66	.	S	802	0904	58	.	S	797	1504	59	.	S	796
0101	70	.	S	806	0905	58	.	S	797	1102	63	.	S	801
0202	70	.	S	806	1001	58	.	S	797	1103	63	.	S	801
0204	70	.	S	806	1002	58	.	S	797	1602	59	.	S	798
1301	60	.	S	797	1003	58	.	S	797	1605	59	.	S	798
1302	60	.	S	797	1004	58	.	S	797					
1303	60	.	S	797	1005	58	.	S	797	E	M	15		
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0902	62	.	S	800	1402	59	.	S	798					
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0905	62	.	S	800						1505	67	.	D	634
1001	62	.	S	800	E	M				1501	67	.	D	644
1004	62	.	S	800	ID	AFP	T	D	AAD	1601	67	.	D	681
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1404	60	.	S	799	1105	63	.	D	246	0803	66	.	D	704
					0401	69	.	D	335	0804	66	.	D	706
E	F	15								1104	62	.	D	723
ID	AFP	T	D	AAD	0701	68	.	D	491	0703	66	.	D	731
					0801	68	.	D	491	0301	69	.	D	734
					1505	59	.	D	563	1603	67	.	D	735
0201	69	.	D	262	0305	69	.	D	588	0405	69	.	D	741
1305	59	.	D	494	1203	63	.	D	609	0705	66	.	D	748
0601	65	.	D	557	0805	68	.	D	614	1105	62	.	D	757
0102	69	.	D	574	1201	63	.	D	626	1201	62	.	D	776
0103	69	.	D	615	1101	63	.	D	637	1504	67	.	D	800
1304	59	.	D	640	1202	63	.	D	637	1502	67	.	S	802
0203	69	.	D	654	1604	59	.	D	634	0404	69	.	S	802
1401	59	.	D	650	0703	68	.	D	646	0801	66	.	S	802
0604	65	.	D	688	1104	63	.	D	676	0803	67	.	S	802
1302	59	.	D	683	0404	69	.	D	730	0805	66	.	S	802
1403	59	.	D	698	1603	59	.	D	725	0807	66	.	S	802
1301	59	.	D	699	1601	59	.	D	739	0809	67	.	S	802
0204	69	.	D	727	0303	69	.	D	762	0811	66	.	S	802
0603	65	.	D	748	1204	63	.	D	765	0813	66	.	S	802
0504	65	.	D	775	1502	59	.	D	766	0815	66	.	S	802
0602	65	.	D	782	1205	63	.	D	781	0817	66	.	S	802
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0501	65	.	S	801	0704	68	.	S	804	0304	69	.	S	805
0502	65	.	S	801	0705	68	.	S	804	0305	69	.	S	805
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0404	69	.	S	805	2202	71	.	D	780	0104	69	.	S	807
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0203	69	.	D	692	1405	71	.	S	807	2503	71	.	S	821
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0505	71	.	D	778	0102	69	.	S	807	2103	71	.	S	837

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ACETONE	M			0	0603	70	.	S	806	1004	71	.	S	834
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0805	71	.	D	743	1704	71	.	S	814	2705	70	.	S	847
3003	71	.	D	743	1705	71	.	S	814	0901	70	.	S	847
2602	71	.	D	759	0801	78	.	S	823	0902	70	.	S	847
2005	71	.	D	759	0802	78	.	S	823	0904	70	.	S	847
1003	71	.	D	760	0803	78	.	S	823	2701	70	.	S	847
1001	71	.	D	766	0701	71	.	D	821	2702	70	.	S	847
1002	71	.	D	771	1701	78	.	D	832	2703	70	.	S	847

2601	71	.	S	856	0203	63	.	S	802	1603	66	.	S	805
2602	71	.	S	856	0204	63	.	S	802	1605	66	.	S	805
2603	71	.	S	856	1304	67	739	S	806	0701	70	.	S	813
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1801	71	.	S	858	1402	67	.	S	806	0803	70	.	S	813
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0702	71	.	S	862	0905	62	.	S	805	1203	60	.	S	804
0703	71	.	S	862	1001	62	.	S	805	1205	60	.	S	804
0704	71	.	S	862	1004	62	.	S	805					
2601	71	.	S	863	0502	68	.	S	811					
2603	71	.	S	863	0603	68	.	S	811					
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1801	71	.	S	865										
1802	71	.	S	865										
1803	71	.	S	865										
1804	71	.	S	865										
1805	71	.	D	865										
					1101	60	.	D	364					
					0403	66	.	D	549					
<b>ACETONE F</b>					0303	66	.	D	592					
					0402	66	.	D	615					
					1604	66	.	D	622					
1002	62	.	D	539	0802	70	.	D	666					
0505	68	.	S	551	0302	66	.	D	683					
1305	67	.	D	606	0405	66	.	D	691					
0501	68	.	D	621	1503	66	.	D	706					
1003	62	.	D	657	1201	60	.	D	712					
1005	62	.	D	672	0703	70	.	D	728					
1403	67	.	D	707	0705	70	.	D	742					
0503	68	.	D	726	1204	60	.	D	739					
0903	62	.	D	722	0704	70	.	D	749					
0602	68	.	D	735	0805	70	.	D	767					
0901	62	.	D	744	0401	66	.	D	784					
0601	68	.	D	755	1202	60	.	D	789					
0504	68	.	S	768	1105	60	.	D	795					
1301	67	.	D	784	0301	66	.	S	805					
1302	67	.	D	784	0304	66	.	S	805					
0205	63	.	D	786	0305	66	.	S	805					
0201	63	.	D	798	0404	66	.	S	805					
0101	63	.	S	802	1501	66	.	S	805					
0102	63	.	S	802	1502	66	.	S	805					
0103	63	.	S	802	1504	66	.	S	805					
0104	63	.	S	802	1505	66	.	S	805					
0105	63	.	S	802	1601	66	.	S	805					
0202	63	.	S	802	1602	66	.	S	805					



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