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MEMORANDUM OF CONFERENCE

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Date: February 13, 1985; June 6, 1985; May 31, 1996

Place: FDA, CFSAN, Washington DC

Purpose: Cancer Assessment Committee Meeting

Subject: Acrylamide

Participants:

CAC Members:

Dr. R. J. Lorentzen, Office of Policy, Planning and Strategic Initiatives (HFS-16); Chairman R. J. Lorentzen 5/5/97

Dr. K. B. Ekelman, Additives Evaluation Branch #2 (HFS-227); Executive Secretary Karen B. Ekelman 5/14/97

Dr. R. W. Moch, Pathology Branch (HFS-716) Robert W. Moch 5 May 97

Dr. P. N. Dua, Pathology Branch (HFS-716) P N Dua 5/5/97

Dr. D. G. Hattan, Division of Health Effects Evaluation (HFS-225) D. G. Hattan 5/9/97

Dr. C. N. Barton, Experimental Design and Evaluation Branch (HFS-706) Curtis Barton 5/6/97

Dr. F. S. Lin, Additives Evaluation Branch #2 (HFS-227) F S Lin 5/7/97

Dr. S. H. Tao, Contaminants Standards, Monitoring and Programs Branch (HFS-308) S-H. Tao 5/12/97

Dr. T. G. Wilcox, Epidemiology Branch (HFS-728) Thomas G Wilcox 5/6/97

Dr. A. B. Bailey, Chemistry Review Branch (HFS-247) Allen B. Bailey 5/9/97

Other Participants:

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The purpose of this meeting was to evaluate the results of two carcinogenicity studies of acrylamide in Fisher 344 rats: the Dow study, published in 1986 (1) and the Tegeris study, published in 1995 (2). Results of these studies were reviewed in several memoranda and documents (3, 4). In response to numerous food additive petitions, polymers made with acrylamide and other components are regulated for 13 food additive uses under 21 CFR (172.255, 173.5, 173.310, 175.105, 175.300, 175.380, 175.390, 176.110, 176.170, 176.180, 177.1010, 177.1210, 178.3520). In addition, there are seven pending petitions in which acrylamide is used in the manufacture of the petitioned food additive (3B3677, 3B3696, 6B3940, 9B4131, 9B4132, 9B4133 and 9A4175).

In the Dow study, 90 CDF Fisher 344 rats/sex/group were given 0 (controls), 0.01, 0.1, 0.5, or 2.0 mg acrylamide/kg bw/day via drinking water for up to two years. Ten rats/sex/group were randomly selected for interim sacrifice after 6, 12, or 18 months on study; the remaining 60 rats/sex/group[1] were scheduled for the two-year terminal sacrifice. In this study, there were statistically significantly increased incidences of rats with the following tumors:

1. High-dose male rats with thyroid follicular adenomas (controls, 1/60 or 2%; 0.01 mg/kg bw/day, 0/58 or 0%; 0.1 mg/kg bw/day, 2/59 or 3%; 0.5 mg/kg bw/day, 1/59 or 2%, 2.0 mg/kg bw/day, 7/59 or 12% [p=0.014 by Peto's mortality adjusted test]); there

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were no male rats with thyroid follicular adenocarcinomas in this study.

2. Male rats with testicular mesotheliomas (control, 3/60 or 5%; 0.01 mg/kg bw/day, 0/60 or 0%; 0.1 mg/kg bw/day, 7/60 or 12%; 0.5 mg/kg bw/day, 11/60 or 18% [p=0.013 by Peto's mortality adjusted test]; 2.0 mg/kg bw/day, 10/60 or 17% [p=0.017 by Peto's mortality adjusted test]) in the two highest dose groups;

3. High-dose female rats with adenocarcinoma of the uterus (controls, 1/60 or 2%; 0.01 mg/kg bw/day, 2/60 or 3%; 0.1 mg/kg bw/day, 1/60 or 2%; 0.5 mg/kg bw/day, 0/59 or 0%; 2.0 mg/kg bw/day, 5/60 or 8% [p=0.025 by Peto's mortality adjusted test]);

4. High-dose female rats with mammary gland fibroadenomas or fibromas (controls, 10/60 or 17%; 0.01 mg/kg bw/day, 11/60 or 18%; 0.1mg/kg bw/day, 9/60 or 15%; 0.5 mg/kg bw/day, 17/58 or 29%; 2.0 mg/kg bw/day, 21/61 or 34% [p=0.007 by Peto's mortality adjusted test]), female rats with mammary gland adenocarcinomas (controls, 2/60 or 3%; 0.01 mg/kg bw/day, 1/60 or 2%; 0.1 mg/kg bw/day, 1/60 or 2%; 0.5 mg/kg bw/day, 2/58 or 3%; 2.0 mg/kg bw/day, 6/61 or 10% [p=0.022 by Peto's mortality adjusted trend test]) and female rats with mammary gland adenoma or adenocarcinoma (controls, 2/60 or 3%; 0.01 mg/kg bw/day, 2/60 or 3%; 0.1 mg/kg bw/day, 1/60 or 2%; 0.5 mg/kg bw/day, 5/58 or 9%; 2.0 mg/kg bw/day, 8/61 or 13% [p=0.01 by Peto's mortality adjusted trend test]);

5. High-dose female rats with brain astrocytomas (controls, 0/60 or 0%; 0.01 mg/kg bw/day, 2/60 or 3%; 0.1 mg/kg bw/day, 1/60 or 2%; 0.5 mg/kg bw/day, 1/60 or 2%; 2.0 mg/kg bw/day, 7/60 or 12% [p=0.006 by Fisher's test]), high-dose female rats with brain tumors of glial origin (controls, 0/60 or 0%; 0.01 mg/kg bw/day, 3/60 or 5%; 0.1 mg/kg bw/day, 2/60 or 3%; 0.5 mg/kg bw/day, 1/60 or 2%; 2.0 mg/kg bw/day, 8/60 or 13% [p=0.003 by Fisher's test]) and high-dose female rats with brain or spinal cord tumors of glial cell origin (controls, 1/60 or 2%; 0.01 mg/kg bw/day, 3/60 or 5%; 0.1 mg/kg bw/day, 2/60 or 3%; 0.5 mg/kg bw/day, 1/60 or 2%; 2.0 mg/kg bw/day, 10/60 or 17% [p=0.004 by Fisher's test]);

Although there was an increased incidence of high-dose female rats with thyroid follicular adenomas or adenocarcinomas (controls, 1/58 or 2%; 0.01 mg/kg bw/day, 0/59 or 0%; 0.1 mg/kg bw/day, 1/59 or 2%; 0.5 mg/kg bw/day, 1/58 or 2%; 2.0 mg/kg bw/day, 5/60 or 8%) in the Dow study, this increase was not statistically significant [p=0.063 by Peto's mortality adjusted test]).

The authors of the Dow study reported increased incidences of high-dose female rats with oral squamous papillomas of the hard palate or lip (controls, 0/9 or 0%; 0.01 mg/kg bw/day, 3/12 or 25%; 0.1 mg/kg bw/day, 2/15 or 13%; 0.5 mg/kg bw/day, 1/9 or 11%; 2.0 mg/kg bw/day, 5/15 or 33%) and increased incidences of high-dose female rats with adenomas of the clitoral gland (controls, 0/2 or 0%; 0.01 mg/kg bw/day, 1/3 or 33%; 0.1 mg/kg bw/day, 3/4 or 75%; 0.5 mg/kg bw/day, 2/4 or 50%; 2.0 mg/kg bw/day, 5/5 or 100%). However, microscopic examination of the hard palate, lip and clitoral gland was performed only for those rats with palpable masses in these tissues. The Cancer Assessment Committee concludes that the significance of these findings cannot be evaluated because neither the total sample size nor the sample size of the selected subset is appropriate to use as the incidence denominator.

Authors of the Dow study also reported increased incidences of high-dose male rats with benign pheochromocytomas of the adrenal gland (controls, 3/60 or 5%; 0.01 mg/kg bw/day, 7/59 or 12%; 0.1 mg/kg bw/day, 7/60 or 12%; 0.5 mg/kg bw/day, 5/60 or

8%; 2.0 mg/kg bw/day, 10/60 or 17%) and increased incidences of high-dose female rats with benign adenomas of the pituitary gland (controls, 25/59 or 42%; 0.01 mg/kg bw/day, 30/60 or 50%; 0.1 mg/kg bw/day, 32/60 or 53%; 0.5 mg/kg bw/day, 27/60 or 45%; 2.0 mg/kg bw/day, 32/60 or 53%). The Cancer Assessment Committee notes that the historical control incidences of Fisher 344 male rats with pheochromocytomas and Fisher 344 female rats with pituitary adenomas are highly variable. For male rats with pheochromocytomas, the average historical control incidence reported by the testing laboratory was 7% [range, 1.2% to 12%] and the average historical control incidence reported by NTP was 17.9%. For female rats with pituitary adenomas, the average historical control incidence reported by the testing laboratory was 35.7% [range, 28.2% to 46%] and historical control incidence reported by NTP was 44% [range, 18% to 70%]). In addition, the Committee notes that the incidences of high-dose male rats with pheochromocytomas (17%) and high-dose female rats with pituitary adenomas (53%) in the Dow study fall within the respective historical control ranges. Thus, the Cancer Assessment Committee concludes that the increased incidences of high-dose male rats with pheochromocytomas and of high-dose female rats with pituitary adenomas in the Dow study represent expected variations in the spontaneous incidences of these tumors in Fisher 344 rats and do not appear to be associated with consumption of acrylamide in drinking water for two years.

The Cancer Assessment Committee concludes that the Dow study is adequate for determining the carcinogenicity of acrylamide. Based on results of the Dow study, the Committee concludes that consumption of drinking water containing up to 2.0 mg acrylamide/kg bw/day for two years by Fisher 344 rats is associated with statistically significantly increased incidences of male rats with thyroid follicular adenomas, male rats with testicular mesotheliomas, female rats with mammary tumors (adenomas or adenocarcinomas; fibromas or fibroadenomas; adenocarcinomas alone), and female rats with central nervous system tumors (brain astrocytomas; brain or spinal cord glial tumors).

The Cancer Assessment Committee notes, however, that the unusually high incidence of control males with brain or spinal cord glial tumors in the Dow study may have obscured the significance of these tumors in acrylamide-treated, high-dose male rats (males: controls, 5/60 or 8%; 0.01 mg/kg bw/day, 2/60 or 3%; 0.1 mg/kg bw/day, 0/60 or 0%; 0.5 mg/kg bw/day, 3/60 or 5%; 2.0 mg/kg bw/day, 7/60 or 12%). The average historical control incidence for males with glial tumors of the central nervous system reported by the testing laboratory was 1% [range, 0% to 2.3%].

In the Tegeris study, groups of Fisher 344 rats were given 0 (Control 1: 102 males and 50 females; Control 2: 102 males and 50 females), 0.1 (204 males), 0.5 (102 males), 1.0 (100 females); 2.0 (75 males), or 3.0 mg acrylamide/kg bw/day (100 females) via drinking water for two years. An additional 25 control rats/sex were used for serological assessment at three month intervals. Because of serious deficiencies in the conduct of the study, the Cancer Assessment Committee considers the Tegeris study to be inappropriate for use in determining the carcinogenicity of acrylamide or for performing a quantitative risk assessment. For example, there is evidence that acrylamide-dosed rats received significantly lower total doses of the test compound than was planned or reported. In spite of this, however, male and female rats had significantly higher incidences of tumors than control rats at some sites for which

tumors also were detected in the Dow study: male rats with thyroid follicular cell adenomas or adenocarcinomas and mesotheliomas of the testicular tunic; female rats with thyroid follicular cell adenomas or adenocarcinomas and mammary gland adenocarcinomas or fibroadenomas. These results lend additional support to the validity of the results obtained in the Dow study.

In conclusion, based on the results of the Dow study, the Cancer Assessment Committee concludes that administration of up to 2.0 mg acrylamide/kg bw/day for two years to Fisher 344 rats via drinking water is associated with significantly increased incidences of male rats with thyroid follicular adenomas, male rats with testicular mesotheliomas, female rats with mammary tumors (adenomas or adenocarcinomas; fibromas or fibroadenomas; adenocarcinomas alone), and female rats with central nervous system tumors (brain astrocytomas; brain or spinal cord glial tumors). The Committee considers the Dow study appropriate for performing a quantitative risk assessment for acrylamide. In contrast, the Committee considers the Tegeris study to be inappropriate for use in determining the carcinogenicity of acrylamide or for performing a quantitative risk assessment, because of serious deficiencies in the conduct of the study.

Karen B. Ekelman 4/28/97

Karen B. Ekelman, Ph.D.
Executive Secretary,
Cancer Assessment Committee

Footnotes:

[1] One female rat given 2.0 mg acrylamide/kg bw/day died the day prior to the scheduled necropsy at 18 months; this animal was included in the 60 animals in the 2.0 mg/kg bw/day dose group scheduled to be sacrificed at the end of the study (2 years), thus, increasing this number to 61 females (Reference 3.A).

[2] Memorandum from C. Barton to K. Ekelman, March 11, 1997; the following tests of statistical significance were used: Fisher's exact test for one dose vs. control; Cochran-Armitage test for dose-response trend; Peto test for one dose vs. control (mortality adjusted); Peto trend test for dose-response trend (mortality adjusted). No statistical significance was calculated for oral or clitoral tumors.

References:

1. Johnson, K.A. et al. 1986. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fisher 344 rats; Toxicology and Applied Pharmacology 85:154-168.

2. Friedman, M.A. et al. 1995. A lifetime oncogenicity study in rats with acrylamide; Fundamental and Applied Toxicology 27: 95-105.

[redacted]

3. Dow study:

A. 2/21/85 Memorandum from L. Taylor to R. Lorentzen, "Request for CAC evaluation of the 2-year drinking water chronic toxicity-oncogenicity study on acrylamide in Fisher 344/N;"

B. 4/29/85 Memorandum from L. Taylor to R. Lorentzen, "Additional carcinogenicity studies on acrylamide; update of DT memo dated 2/21/85;"

C. 11/5/85 Memorandum from L. Taylor to R. Lorentzen, "Clarification of the number of animals with various tumors reported in a drinking water study on acrylamide; update on DT memo dated 2/21/85--request for CAC evaluation of study;"

D. Frankos, V; 1985; "Critical review of acrylamide's carcinogenic activity in Fisher 344 rats: design of a new cancer bioassay in rats;"

E. 4/23/86 Memorandum from L. Taylor to R. Lorentzen, "Protocol for lifetime oncogenicity study with acrylamide in rats; request of Cancer Assessment Committee review;"

F. 4/30/96 Memorandum from M. Bonner to K. Ekelman: "Review of Environ Corporations's 'Critical Review of Acrylamide's Carcinogenic Activity in Fisher 344 Rats'."

G. 9/7/95 Memorandum from M. Bonner to K. Ekelman: "Dow chronic study on acrylamide; comparison of tumor incidences reported in published article and in Dr. Taylor's draft CAC review."

H. 4/26/96 Memorandum from M. Bonner to K. Ekelman: "Addendum to draft: Dow chronic study on acrylamide; comparison of tumor incidences reported in published article and in Dr. Taylor's draft CAC review."

I. 11/21/96 Memorandum from M. Bonner to K. Ekelman: "Real treatment effects reported in Dow bioassay with acrylamide."

J. 3/10/97 Draft memorandum from M. Bonner to K. Ekelman: "Significant tumor incidences reported in Dow bioassay on acrylamide that are substantial treatment induced effects."

K. 3/11/97 Memorandum from C. Barton to K. Ekelman: "Statistical analysis of acrylamide data for CAC."

4. Tegeris study:

A. 2/5/96 Memorandum from K. Misra to K. Ekelman: "A lifetime oncogenicity in rats with acrylamide," Study no. 85033 performed by Tegeris Laboratories of Temple Hills, MD.

B. 1/25/96 Memorandum from J. Welsh, C. Whiteside, L. Pellicore and M. Bonner to K. Ekelman: "Review of data audit findings for 'A Lifetime Oncogenicity Study With Acrylamide' sponsored by American Cyanamid Co. of Wayne, NJ."

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