AD

April 10, 1998

REPORT OF THE QUANTITATIVE RISK ASSESSMENT COMMITTEE

Subject: Assessment of carcinogenic upper-bound lifetime risk for acrylamide resulting from contamination by acrylamide of copolymers, intended for use as retention aids, drainage aids, stabilizer or ~~fixing~~ agents in paper and paperboard contacting foods (FAP 6B3677, 6B3696, 6B3940, 9B4131, 9B4132, 9B4133, and 9A4175, Calgon Corp., National Starch & Chemical Corp., American Cyanamid Corp., Lubrizol Corp., Lubrizol Corp., Lubrizol Corp. and Enzyme Bio-Systems Ltd., respectively)

The Quantitative Risk Assessment Committee (QRAC) has been requested to estimate the carcinogenic upper-bound lifetime risk for acrylamide which impacts on the previously mentioned food additive petitions.

The Cancer Assessment Committee (CAC) in its memorandum written April 4, 1997 (Ekelman, K.B., Ph.D., April 4, 1997, Cancer Assessment Committee meeting on acrylamide) concluded, based on the results of a study sponsored by Dow (Johnson et al., 1986), that administration of up to 2.0 mg acrylamide/kg body weight /day for two years to Fischer 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 rat with central nervous system tumors (brain astrocytomas, brain or spinal cord glial tumors) and female rats with uterine tumors (adenocarcinomas). The Committee considers the Dow study appropriate for performing a quantitative risk assessment for acrylamide. The Committee does not consider the Tegeris study (Friedman et al., 1995) to be appropriate 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.

Table 1 summarizes the CAC's determination of statistically significant increases in tumors as a result of exposure to acrylamide in a 2-year rat drinking water bioassay.

Table 1. Increases in Tumors in Fisher 344 Rats as a Result of Exposure to Acrylamide in a 2-year Rat Drinking Water Bioassay

		Dose (mg/kg/day)				
Tumor	**Sex**	**0**	**0.01**	**0.1**	**0.5**	**2.0**
thyroid follicular adenomas	male	1/60 (2%)	0/58	2/59 (2%)	1/59 (2%)	7/59 (12%)
testicular mesothe-lioma	male	3/60 (5%)	0/60	7/60 (12%)	11/60 (18%)	10/60 (17%)
mammary						
adenomas/ adenocarc.	female	2/60 (3%)	2/60 (3%)	1/60 (2%)	5/58 (9%)	8/61 (13%)
fibromas/ fibroade-nomas	female	10/60 (2%)	11/60 (18%)	9/60 (15%)	17/58 (33%)	21/61 (34%)
adenocarc. alone	female	2/60 (3%)	1/60 (2%)	1/60 (2%)	2/58 (3%)	6/61 (10%)
central nervous system tumors						
brain or spinal cord astrocytoma	female	0/60	2/60 (3%)	1/60 (2%)	1/60 (2%)	7/60 (12%)
brain or spinal cord glial tumors	female	1/60 (2%)	3/60 (5%)	2/60 (3%)	1/60 (2%)	10/60 (17%)
uterus adenocarc.	female	1/60 (2%)	2/60 (3%)	1/60 (2%)	0/59	5/60 (8%)

To estimate unit risks, the QRAC decided to use a linear

extrapolation from the dose of acrylamide which showed a significant effect (not necessarily a statistically significant effect) in comparison to a zero dose. A sample calculation is shown below for an extrapolation from the 2.0 mg/kg bw/d dose level and the male rat thyroid follicular adenomas.

Male rat thyroid follicular adenomas at 2.0 mg/kg/d dose level:

Subtracting tumors in controls 7-1 = 6,

$$\text{then unit risk} = \frac{6/59 \text{ animals}}{2.0 \text{ mg/kg bw/d}} = \frac{0.10}{2.0} = 5 \times 10^{-2} \text{ (mg/kg/d)}^{-1}$$

Exposures to acrylamide from the subject petitions have been summarized in Table 2 (attached) from the Scientific Support Branch (HFS-207) memorandum of August 7, 1997 (A.B.Bailey, Ph.D. (HFS-207) to D. Harrison (HFS-215), August 7,1997, FAPs 9A4175, 3B3677, 6B3940, 3B3696, 9B4131, 9B4132, and 9B4133, DPC request to identify and address unresolved issues in the pending acrylamide petitions).

Total risks for male and female significant tumors were summed; sample calculations are shown below for FAP 3B3677.

Table 3. Unit Risks, Exposure and Upper Bound Lifetime Risks for Significant Male and Female Tumors for FAP 3B3677

Tumor type	Unit Risk	Exposure (mg/kg bw/day)	Upper bound lifetime risk
Male thyroid	5×10^{-2}	1.8×10^{-6}	9.0×10^{-8}
Male testicular	6.7×10^{-1}	1.8×10^{-6}	1.2×10^{-6}
Total male tumors	7.2×10^{-1}		1.3×10^{-6}
Female mammary	3.4×10^{-1}	1.8×10^{-6}	6.1×10^{-7}
Female (total CNS tumors)	1.3×10^{-1}	1.8×10^{-6}	1.4×10^{-7}
Female uterus	3.3×10^{-2}	1.8×10^{-6}	5.9×10^{-8}
Total female tumors	5.0×10^{-1}		9.0×10^{-7}

Table 4 shows upper bound lifetime risks for the exposures to acrylamide from the subject petitions using the unit risk estimates

for total male rat tumors and total female rat tumors. Exposures for petitions 9B4132 and 9B4133 were the same; 6B3940 was a substitutional exposure.

Table 4. Upper Bound Lifetime Risks for Exposures to Acrylamide from Subject Petitions Based on Unit Risks Estimated from Total Significant Male Rat Tumors and Total Significant Female Rat Tumors

Exposure mg/kg bw/day	9A4175 6.8×10^{-7}	3B3677 1.8×10^{-6}	3B3696 1.7×10^{-6}	9B4131 1×10^{-8}	9B4132/ 9B4133 2.5×10^{-9}
Risk estimate (Total male tumors)	4.9×10^{-7}	1.3×10^{-6}	1.2×10^{-6}	7.2×10^{-9}	1.8×10^{-9}
Risk estimate (Total female tumors)	3.5×10^{-7}	9.0×10^{-7}	8.7×10^{-7}	5.1×10^{-9}	1.3×10^{-9}

Conclusions

QRAC found the dose-response curves plotted for the statistically significant tumors to be quite flat, which could indicate that acrylamide is not a particularly potent carcinogen under the conditions of the assay and in the Fisher rat. In addition, the exposures to acrylamide from the subject petitions were noted by QRAC to be conservative. A range of upper bound risk estimates are given in Table 4 based on the carcinogenic potency of acrylamide as based on total male or total female rat tumors.

a- includes monomers and other impurities;
b- based on virtually nil exposure;
c- exposure from use in adhesives (§175.105) and in paper coatings for dry food (§176.180) was concluded to be virtually nil, or < 150 μg/p/d;
d- combined exposure from use in adhesives (§175.105) and in paper coatings for dry food (§176.180)

Table 2: Summary of Exposure Estimates for AM

FAP	Regulation	Polymer	AM EDI
9A4175	173.357	AAR	41 ng/p/d
3B3677	176.170	DADMAC/AM	0.11 μg/p/d
6B3940	176.180	AM/AMPS, Na salt	substitutional
3B3696	176.180	DADMAC/AM/AA, Na salt	0.1 μg/p/d
9B4131	176.170	AMPS	0.6 ng/p/d
9B4132/ 9B4133	176.180/ 175.105	AMPS	0.15 ng/p/d[a]

a- combined exposure from use in adhesives (§175.105) and in paper coatings for dry food (§176.180)

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HFS-206 (Tarantino); 226; 245; 246 (Kuznesof, Reading File)
HFS-207:ABBailey:418-3007:abb:6-24-97
Rerough: 7-16-97
RDInit: MAAdams, 7-25-97
LIBararseh, 8-5-97
Final:lsl:8-7-97

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References

Friedman, M.A., Dulak, L.H., and Stedham, M.A.(1995). A lifetime oncogenicity study in rats with acrylamide. Fund., Appl. Toxicol. **27**:95-105.

Johnson, K.A., Gorzinski, S.J., Bodner, K.M., Campbell, R.A., Wolf, C.H., Friedman, M.A., and Mast, R.W. (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol. Appl. Pharmacol. **85**:154-168.

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TABLE I

Residual Acrylamide in 50/50 DMDAAC/Acrylamide Copolymers (1998)

85 Batches

Number of Batches	Residual Acrylamide (% Based on Polymer)
83	≤0.06%
1	0.10%
1	0.14%