

## Carcinogenic Effects of Acrylamide in Sencar and A/J Mice

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### ABSTRACT

Acrylamide structurally resembles vinyl carbamate, a proposed proximate carcinogenic form of ethyl carbamate. To test the hypothesis that acrylamide should possess carcinogenic properties, it was tested in the *Salmonella*-microsome assay for point mutation, as a skin tumor initiator in the Sencar mouse, and for its ability to induce lung adenomas in the A/J mouse. Acrylamide was found to be without activity as a mutagen in *Salmonella* strains TA 1535, TA 1537, TA 98, and TA 100 both in the presence and absence of rat liver microsomes using both the plate and liquid suspension assays. However, acrylamide was found to approximate ethyl carbamate in potency as a tumor initiator in the skin of the female Sencar mice. As with ethyl carbamate, acrylamide was more potent by systemic routes of administration relative to topical application. Acrylamide was also found to induce lung adenomas in male and female A/J mice using both the p.o. and i.p. routes of administration. Acrylamide was approximately one-seventh as potent as ethyl carbamate in the induction of lung adenomas. These data confirm the hypothesis that acrylamide possesses carcinogenic properties similar to ethyl carbamate.

### INTRODUCTION

Acrylamide is a chemical widely used in the synthesis of a variety of polymers. Some of these polymers are used as coagulant aids in the treatment of drinking water (6). Polymers used for this purpose are restricted to an acrylamide monomer content of 0.05% based upon the well-known neurotoxic properties of acrylamide (7, 13).

Acrylamide bears a striking structural resemblance to VC,<sup>2</sup> a chemical which has been suggested as the proximate carcinogenic form of EC (urethan). The only difference in structure between the 2 chemicals is a single oxygen atom (Chart 1). VC has been demonstrated as a more potent carcinogen than EC in both the mouse skin and mouse lung, which are classical target organs for EC (5). Recent research has revealed that etheno- and 2-oxoethyl adducts to purine and pyrimidine bases in DNA are formed in the liver of the rat following EC treatment (9). On the basis of this close structural resemblance to an established carcinogen, we have postulated that acrylamide should be carcinogenic in mouse skin and lung. The present study is presented as a test of that hypothesis.

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<sup>2</sup> The abbreviations used are: VC vinyl carbamate; EC ethyl carbamate; TPA, 12-O-tetradecanoyl-phorbol-13-acetate; S-9, 9000 × g supernatant from a liver homogenate; EPA, Environmental Protection Agency; MCO, Medical College of Ohio.

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### MATERIALS AND METHODS

**Chemical.** Acrylamide was obtained from Eastman Kodak Chemical Co., Rochester, N. Y., and was assayed at greater than 99% purity by linked gas chromatographic and mass spectrometric analysis (Chart 2). EC was obtained from MC&B Manufacturing Chemists and was certified to be 98% pure. TPA was purchased from Chemical Carcinogenesis Co., Eden Prairie, Minn.

**Assay for Mutagenic Activity.** The standard plate test method for the *Salmonella*-microsome assay as described by Ames *et al.* (2) was used to test the potential mutagenic activity of acrylamide. A liquid preincubation modification of this method was also used in which a 30-min liquid preincubation of test ingredients at 37° was included prior to addition of the top agar. In both cases, acrylamide was tested with *S. typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100. The strains were a gift of Dr. Bruce Ames (University of California, Berkeley, Calif.). Assays were conducted with half-log dose levels ranging from 0.001 to 3 mg in an initial assay and from 3 to 30 mg in a repeat assay. Duplicate platings were made at each test dose. Assays were performed both with and without metabolic activation. An S-9 fraction from Arochlor-induced male Sprague-Dawley rats was used for activation. The procedures for preparation of the S-9 fraction and S-9 cofactor mix were those used by Ames *et al.* (2). The concentration of S-9 used was 50 μl of S-9 fraction per ml of S9 mix. Negative and positive controls were included with each assay. The positive controls were: (a) without activation, sodium azide for strains TA 1535 and TA 100, 2-nitrofluorene for TA 98, and 9-aminoacridine for TA 1537; and (b) with activation, 2-aminoanthracene for all strains.

**Mouse Skin Initiation-Promotion Assay.** Female Sencar mice were obtained from Dr. T. Slaga of Oak Ridge National Laboratories, Oak Ridge, Tenn. Animals from 6 to 8 weeks of age were placed in groups of 40 for acrylamide exposure and of 25 for EC treatment. Both chemicals were administered by 3 separate routes: gastric intubation; i.p. injection; and topically to the shaved back. Acrylamide was dissolved in distilled water for the p.o. and i.p. administration and in ethanol for the topical application. EC was dissolved in 10% emulphor (polyoxygenated vegetable oil) for p.o. and i.p. routes and in acetone for topical application. Control animals (40/group) received equivalent volumes of the appropriate solvents. Acrylamide was tested at doses of 12.5, 25.0, or 50.0 mg/kg for 6 applications over a 2-week period for total doses of 75, 150, and 300 mg/kg. This technique avoided the complication of overt peripheral neuropathy generally observed with doses that exceed 50 mg/kg. EC was delivered in one application at doses of 30, 100, and 300 mg/kg. Two weeks following these tumor-initiating doses of both acrylamide and EC, a tumor promotion regimen was begun, wherein 1.0 μg TPA in 0.2 ml acetone was applied to the shaved back of each animal 3 times/week for 20 weeks. Control groups (20/group) for promotion received 0.2 ml acetone at the same frequency and duration of treatment.

Tumor incidences were charted from weekly observation. To be included in the cumulative count, an animal must have had a tumor of more than 1 mm diameter in the same location for 3 consecutive observations. All animals were sacrificed at 52 weeks in the study, and histopathological evaluations were done on all gross lesions.

**Mouse Lung Adenoma Bioassay.** The mouse lung adenoma experiments were conducted at 2 different laboratories. Strain A/J mice used in the tests at the EPA Laboratory were obtained from Harlan Sprague-

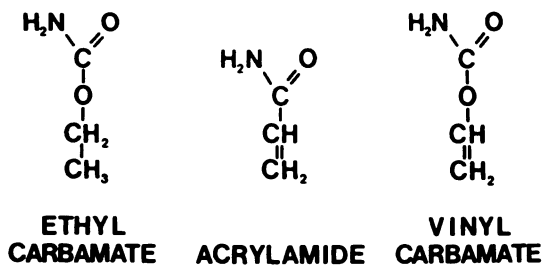


Chart 1. Structural resemblance of acrylamide to VC, the proposed proximate carcinogenic form of EC.

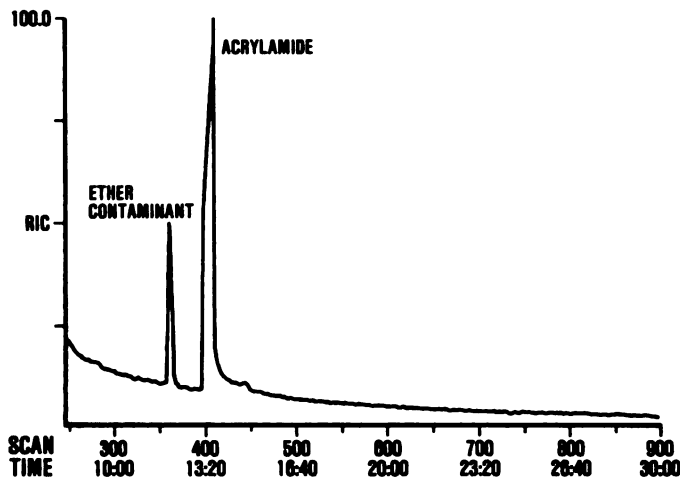


Chart 2. Reconstructed gas chromatograph of acrylamide used in the present studies. Acrylamide (500 ng) dissolved in 2 µl diethyl ether was injected onto a 60-m x 0.2-mm (inside diameter) SE 30 fused silica capillary column at an injector temperature of 260°. Oven temperature was 20° for 6 min and was then programmed at 2°/min. The detector was a Finnigan 3300 quadrupole mass spectrometer, and the scan time was 2 sec. The peak labeled ether contaminant could be entirely accounted for in the solvent.

Dawley, Inc., Indianapolis, Ind. Those tested at the laboratories of the MCO were available from their own breeding colony. At EPA, groups of 80 (40 male and 40 female) mice, 8 weeks old, received p.o. doses of 6.25, 12.5, or 25.0 mg of acrylamide per kg body weight 3 times/week for 8 weeks. EC was administered to the same number of mice per group at dose levels of 10.5, 21.0, and 42 mg/kg, and at the same frequency and duration of treatment. Since both chemicals were dissolved in distilled water, the control group received distilled water at the same volume and duration as for the test compounds (0.2 mg/administration). At MCO, groups of 32 (16 male and 16 female) mice, 8 weeks old, received i.p. injections of 1, 3, 10, 30, or 60 mg of acrylamide per kg, 3 times/week for 8 weeks. For comparison with results at EPA, a group was included which received acrylamide 30 mg/kg p.o. with the same treatment schedule. Two base-line control groups were included: an untreated group; and a vehicle control group that received i.p. injections of distilled water. Positive control groups received a single i.p. injection of EC at dose levels of 500 and 1000 mg/kg.

Animals were sacrificed when either 9 months (EPA) or 8 months (MCO) of age, their lungs were fixed in 10% buffered formalin (EPA) or Tellyesniczky's solution (MCO), and the surface adenomas were counted after 24 hr (15).

## RESULTS

Table 1 presents data obtained when acrylamide was tested for mutagenic activity in the *Salmonella*-microsome plate assay described by Ames et al. (2). Acrylamide failed to give a response in any strain with or without the addition of S-9, and with up to

30 mg added per plate. Even at this high dose, there was no obvious evidence of cell killing, as judged by the appearance of a normal background bacterial lawn. Thus, the negative mutagenicity results are apparently not attributable to cytotoxic interferences. Since acrylamide could react with the agar and thus not be available to the bacteria, it was also assayed using a preincubation modification of the standard plate assay. In this procedure, the bacteria are exposed in liquid suspension for 30 min prior to the addition of agar. The results obtained with this procedure also indicated no evidence of mutagenic activity for acrylamide (data not shown).

The dose-response relationship of acrylamide-induced skin tumors in Sencar mice is compared with that of EC in Chart 3. Both chemicals were tested by 3 routes of exposure: p.o.; i.p.; and topical. There was a highly significant dose-response relationship for time to first tumor (Chart 4) as well as the appearance of multiple tumors (Chart 3) by all 3 routes [ $p < 0.01$  by Cox regression model (4, 8)]. Neither EC nor acrylamide increased tumor yield in the absence of TPA promotion (i.e., triweekly application of acetone for 20 weeks). EC is clearly more potent

Table 1  
Evaluation of acrylamide for mutagenicity in the *Salmonella*-microsome assay

Dose (mg/plate)	Mean His <sup>+</sup> revertants/plate							
	TA1535		TA1537		TA98		TA100	
	-S9*	+S9	-S9	+S9	-S9	+S9	-S9	+S9
<b>Experiment 1</b>								
0.000	17	11	6	6	20	37	172	150
0.001	12	14	8	5	20	36	168	128
0.003	20	14	6	7	18	31	174	152
0.010	15	11	8	5	20	44	179	146
0.030	23	13	7	9	17	39	141	141
0.100	22	11	5	7	23	37	162	149
0.300	21	9	8	7	22	39	175	147
1.000	22	10	6	4	18	25	174	147
3.000	17	11	4	9	13	33	176	134
<b>Experiment 2</b>								
0.0	14	10	6	17	14	24	97	97
3.0	18	6	8	16	11	22	80	104
10.0	12	9	7	21	12	27	88	95
30.0	14	9	7	8	16	29	87	109

\* Indicates whether assay was conducted in the presence (+S9) or absence (-S9) of a 9000 x g supernatant of a rat liver homogenate as described in "Materials and Methods."

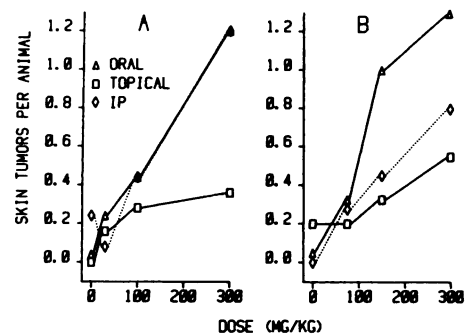


Chart 3. Initiation of skin tumors in female Sencar mice by acrylamide. Results expressed as mean cumulative tumor counts observed in a 52-week observation period. Acrylamide was administered to 40 animals in each group in 6 doses, totaling the amount indicated dissolved in 0.2 ml distilled water for p.o. and i.p. routes or ethanol for topical application. Two weeks following the last dose, a promotion schedule was begun that used a triweekly application of 1.0 µg TPA in 0.2 ml acetone for 20 weeks. No tumors were observed in animals treated at the highest dose by each route in the absence of TPA promotion (data not shown). Experiments with EC were conducted under the same conditions, except that only 25 animals were used per experimental group. A, results with EC; B, results with acrylamide.

by the systemic route of exposure than when applied topically, achieving approximately 5 times the overall tumor yield by the p.o. and i.p. routes as compared to the topical route. Acrylamide displays the same general pattern, except that administration by the p.o. route results in a greater tumor yield than the i.p. as well as the topical route of administration. Statistically, this was reflected in a significantly shorter time to first tumor by the p.o.

versus the topical ( $p \ll 0.01$ ) and i.p. ( $p \ll 0.01$ ) routes at equivalent doses. Acrylamide was observed to be slightly more potent than EC by the p.o. and topical routes, but less potent by the i.p. route of administration.

Table 2 summarizes the types of skin tumors observed in animals that died during this experiment or were sacrificed at the termination of the experiment. The total tumor yield is less than indicated in Chart 3 because it includes only tumors observed at the death of the animal and not tumors that regressed. Animals lost to necropsy because of either autolysis or cannibalism account for the remaining differences in the data. Nevertheless, a dose-response relationship is observed whether the data are expressed as the proportion of initiated animals that bear tumors or as the percentage of animals examined histologically that had squamous cell carcinomas. As was observed with squamous cell papillomas, the yield of squamous cell carcinomas as a function of the route of exposure was: p.o. > i.p. > topical. The yield of malignant tumors observed by the p.o. route of administration of acrylamide closely approximates the yield observed with equivalent doses of EC.

Results from bioassays of acrylamide in the mouse lung are presented separately by route of administration. In Chart 5, the yield of lung adenomas in A/J mice treated with acrylamide by the p.o. route of administration is compared to EC by the same route. Acrylamide increased the yield of lung adenomas in both sexes in a dose-related manner. The dose-response relationship was highly significant ( $p \ll 0.01$ ) when both animals with tumors and the multiplicity of tumors were tested using a logit regression model analysis (4). The tumor yield in males was slightly but consistently higher than in females, although this difference was not statistically significant. This same tendency was observed

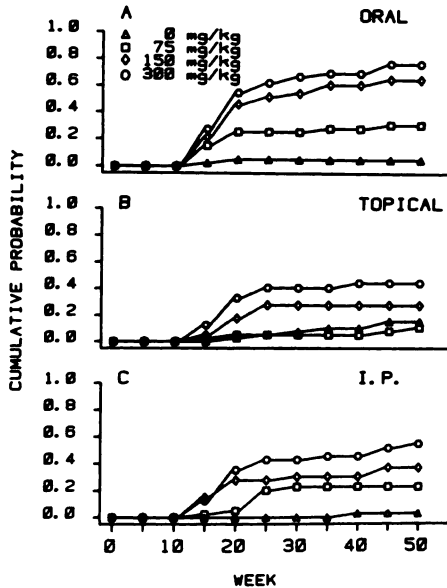


Chart 4. Kaplan-Meier estimates of the probability of first skin tumor occurrence versus time in female Sencar mice for each route of acrylamide administration and each dose group. A, p.o. administration; B, topical application to the shaved back; C, i.p. administration.

Table 2

Tumor-bearing animals and classification of histologically examined skin tumors in Sencar mice initiated with acrylamide by various routes

Dose (mg/kg)	Route of administration	TPA	Cumulative no. of tumor-bearing animals <sup>a</sup> /no. of animals initiated	No. of squamous cell Papillomas/no. of animals examined	No. of squamous cell carcinomas/no. of animals examined	% of animals bearing squamous cell carcinomas
EC						
300	p.o.	+	8/20	0/16 <sup>b</sup>	3/16 <sup>b</sup>	18.8
Acrylamide						
0 <sup>c</sup>	p.o.	+	2/40	0/34	0/34	0
75	p.o.	+	12/40	3/35	2/35	5.7
150	p.o.	+	23/40	8/33	7/33	21.2
300	p.o.	+	30/40	11/38	6/38	15.8
0 <sup>c</sup>	p.o.	-	0/20	0/17	0/17	0
0 <sup>c</sup>	i.p.	+	0/40	0/35	0/35	0
75	i.p.	+	10/40	2/38	2/38	5.2
150	i.p.	+	13/40	3/36	4/36	11.1
300	i.p.	+	21/40	6/35	4/35	11.4
0 <sup>c</sup>	i.p.	-	0/20	0/17	0/17	0
0 <sup>d</sup>	Topical	+	7/40	5/36	0/36	0
75	Topical	+	4/40	3/38	1/38	2.6
150	Topical	+	11/40	3/35	2/35	5.7
300	Topical	+	18/40	2/34	3/34	8.8
300	Topical	-	0/20	0/20	0/20	0

<sup>a</sup> To be included in the cumulative count, the animal must have had a lesion, 1 mm in diameter, for 3 consecutive weekly observations.

<sup>b</sup> Number of animals available for histological examination following death, or at termination of the experiment at 1 year; number excludes heavily autolyzed and cannibalized animals.

<sup>c</sup> Distilled deionized water was administered in the same volume (0.2 ml/mouse) and frequency as used in experimental groups.

<sup>d</sup> Ethanol was administered topically in the same volume (0.2 ml/mouse) and frequency as used for experimental groups.

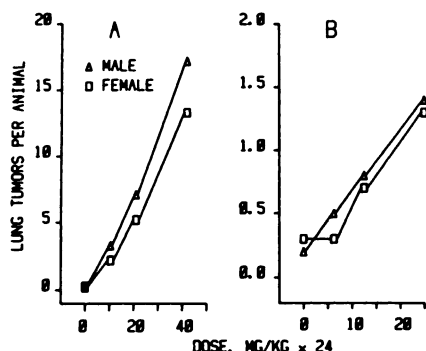


Chart 5. Dose-response relationship of acrylamide-induced lung adenomas in A/J mice. Both acrylamide and EC were administered at the indicated doses to 40 male and 40 female mice 3 times/week for 8 weeks [note the differences in scale (abscissa)]. Animals were sacrificed at 9 months of age, 7 months following the beginning of the experiment. Points, average number of surface adenomas observed per animal. A, results with EC; B, results with acrylamide.

Table 3  
Effects of acrylamide administered i.p. on development of lung tumors in A/J mice

Treatment	Sex	No. of survivors/initial no. of mice	% of mice with lung tumor	Av. no. of lung tumors/mouse
None	M	16/16	31	0.31 ± 0.48 <sup>a</sup>
	F	14/16	50	0.50 ± 0.52
	M + F	30/32	40	0.40 ± 0.50
Distilled H <sub>2</sub> O	M	16/16	13	0.06 ± 0.25
	F	15/16	8	0.13 ± 0.35
	M + F	31/32	10	0.10 ± 0.30
EC	M	10/10	100	13.0 ± 4.9
	F	17/17	100	12.6 ± 3.7
	M + F	27/27	100	12.7 ± 4.1
1000 mg/kg	M	16/16	100	29.8 ± 8.3
	F	13/13	100	32.5 ± 7.0
	M + F	29/29	100	30.9 ± 7.7
Acrylamide 1 mg/kg <sup>b</sup>	M	16/16	50	0.75 ± 0.93
	F	17/17	35	0.35 ± 0.60
	M + F	33/33	42	0.55 ± 0.78
3 mg/kg <sup>b</sup>	M	16/16	38	0.69 ± 1.03
	F	17/17	53	0.88 ± 1.11
	M + F	33/33	46	0.79 ± 1.05
10 mg/kg <sup>b</sup>	M	17/17	59	0.88 ± 0.99
	F	14/15	79	1.57 ± 1.79
	M + F	31/32	68	1.19 ± 1.40
30 mg/kg <sup>b</sup>	M	15/16	93	1.87 ± 1.55
	F	15/16	93	2.53 ± 1.48
	M + F	30/32	93	2.20 ± 1.52

<sup>a</sup> Mean ± S.D.  
<sup>b</sup> Given 3 times/week for 8 weeks.

with EC-treated animals. However, acrylamide only gave rise to about one-seventh of the net tumor yield per unit dose than was observed with EC.

Table 3 summarizes results from experiments using the i.p. route of acrylamide administration in A/J mice. As was observed with p.o. administration, the number of lung adenomas increased with the dose of acrylamide up to 30 mg/kg. Again, the dose-response relationship was found to be statistically significant ( $p < 0.01$ ) by a logit regression model (3). A higher dose, 60 mg/kg, was also attempted, but frank peripheral neuropathy and decreased survival forced termination of the treatment after the 11th injection. Within the context of this same experiment, a parallel group of 14 males and 18 females was treated with 30

mg of acrylamide per kg by the p.o. route of administration for comparative purposes. Eleven surviving males were found to average 2.27 lung tumors/animal, and the 18 females averaged 1.61 lung tumors/animal for an average tumor yield of 1.78 tumors/animal. This latter figure is consistent with a reasonable extrapolation of the doses used in the experiment depicted in Chart 5. Therefore, in terms of lung tumor production, it can be concluded that acrylamide is slightly more potent by the i.p. relative to the p.o. route of administration.

### DISCUSSION

These data clearly establish that acrylamide is capable of increasing the tumor yield in mice. In the skin, this was observed as an increase in the number of malignant, squamous cell carcinomas as well as an increase in the number of papillomas. Despite the fact that acrylamide failed to induce point mutations in the *Salmonella*-microsome assay, it was shown to be capable of acting as a tumor initiator in Sencar mouse skin by 3 different routes of administration in a modified initiation-promotion protocol. The major modification to the usual initiation-promotion protocol was the division of the initiating treatment into 6 doses applied over a 2-week period. This was necessary to avoid the peripheral neuropathy classically associated with acrylamide exposures (13). Gross signs of peripheral neuropathy were not observed in animals in which treatment was limited to 30 mg/kg at 3 times/week or below. This, of course, does not exclude the possibility of more subtle impairments of function.

Although acrylamide was found to be negative in the *Salmonella*-microsome assay, it has been shown to produce aneuploid and polyploid cells in both bone marrow cells and spermatogonia of mice (11). Therefore, it would appear that acrylamide possesses the genotoxic activity (in this case, as a clastogen) thought to be necessary for the initiation of cancer.

Increased tumor yields in the lung with acrylamide treatment can be viewed in the context of an acceleration of the development of these tumors, since A/J mice usually develop from 1 to 2 lung tumors/animal at 1.5 years of age (10, 14). However, considering the fact that acrylamide is capable of initiating tumors in the mouse skin as well, results in the A/J mouse suggest strongly that acrylamide is likely to be capable of acting as a whole carcinogen.

It is interesting to note the implications that these data have for the mechanism of EC carcinogenesis. Acrylamide bears a close structural resemblance to VC with particular respect to the location of the double bond within the molecule. The target organs of acrylamide appear to be analogous to those of EC. Recent data have demonstrated that EC is capable of producing increased sister chromatid exchanges when administered to mice *in vivo* (1), and acrylamide has been shown previously to induce chromatid exchanges in spermatogonia of mice (11). Previously, EC has been routinely found negative in the *Salmonella*/microsome assay, but has been positive in cytogenetic assays conducted either *in vitro* or *in vivo* (12). Consequently, the present results provide indirect evidence that VC may be the proximate carcinogen in EC-induced cancer. In terms of potency, acrylamide closely approximates that of EC in the mouse skin and is about 15% as potent as EC in the mouse lung. The greater effectiveness of both chemicals in the mouse skin by systemic

routes of administration has also been observed with VC (5). This poses an interesting pharmacokinetic problem that is currently under investigation.

In summary, the present work has demonstrated for the first time that acrylamide possesses carcinogenic properties. While acrylamide was apparently not capable of producing point mutations in *Salmonella*, it was capable of acting as a tumor initiator in the mouse skin. In addition, acrylamide increased the lung tumor yield in the strain A/J mouse independent of promoting agents. Together, these data suggest that the carcinogenicity of acrylamide deserves a more thorough evaluation.

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