April 23, 1956

Dr. Hymin Shapiro
Ethyl Corporation
1600 West Eight Mile Road
Ferndale 20
Detroit, Michigan

Dear Doctor Shapiro:

The information which we have concerning the toxicity of APR-128 is as follows:

Signs of Illness

When absorbed in sufficient concentrations into the tissues of rabbits and rats, APR-128 induced signs of illness which were characterized by initial mild excitement and hyperactivity, tremors, severe tonic spasms, weakness, slow and labored respiration, occasional feeble clonic convulsions and terminal coma. Animals that were given sublethal amounts of the compound showed these signs to less extent and in addition generally showed mild transient losses in body weight. Female rats were somewhat more susceptible than were male rats to the toxic effects of the compound.

Intravenous Toxicity

When given intravenously to rabbits as 5 per cent solutions in peanut oil, the lethal dose of APR-128 was 5.0 mg. per kg. body weight irrespective of the sex of the animals (Table 1). One male that was given this dose died after 18 days and in this instance death may have resulted from some secondary infection. Two other rabbits died within a few hours after they were given equivalent amounts of the compound.

Oral Toxicity

The compound was given orally to male and female rats as 2 per cent solutions in peanut oil. The results are summarized in Table 2. Approximately 180 mg. of APR-128 per kg. body weight was lethal to the males. Amounts of the compound that were lethal to females ranged from 16 to 120 mg. per kg., with 55 mg. per kg. probably representing the average lethal dose.

Percutaneous Toxicity

When APR-128 was allowed to remain in contact with the intact abdominal skin of rats for 6 consecutive hours, 940 mg. per kg. was lethal to male rats (Table 3). The lethal dose for the females ranged from 420 to 940 mg. per kg. body weight. The compound seemed to be mildly irritating to the skin but the effects were transient; when the compound was washed from the skin of the animals, no gross evidence of local injury was found.

The Toxicity of Vapors of APR-128

Table 4 contains a summary of the data pertaining to the toxicity of the vapors of APR-128. Four experiments were performed in which rats were supplied with air saturated at temperatures of 24, 28, 33 and 37 degrees, respectively, with vapors of the compound. Female rats were confined individually in a glass chamber (5.8 liters in capacity), through which the saturated air was circulated. The chamber was maintained at the same temperature as that at which the air was saturated.

The first column of Table 4 indicates the consecutive minutes of an exposure period. The second column shows the theoretical percentage ratio of the atmospheric concentration of the compound in the inhalation chamber to that in the air supplied. The other columns show the probable atmospheric concentrations of the compound in the inhalation chamber throughout the course of each of the 4 experiments.

Air saturated with the compound in its gaseous phase was estimated to contain 1.48 mg. per liter at 24° C., 1.71 mg. per liter at 28° C., 2.73 mg. per liter at 33° C., and 3.33 mg. per liter at 37° C. These concentrations were lethal to female rats; the length of the period of exposure required to cause death being 6 hours at 1.48 mg. per liter. As the concentration was increased, the length of the period of survival decreased.

Comments

In Table 5 the toxicity of APR-128 is compared with that of APR-122. The signs of illness induced in experimental animals by the two compounds are similar. Both compounds elicit differential responses in the two sexes. The intravenous and vapor toxicity both indicate that APR-122 may be 2 to 3 times as toxic as APR-128. However, when the compounds were absorbed from the intestinal tract or through the intact skin, the difference was not so obvious.

From the aspects of safety in making and working with these compounds, both must be considered potentially dangerous and the customary safeguards rigorously observed. Particular care should be taken to prevent any inhalation of the vapors of either material.

If you can inform us as to the molecular weights of APR-122 and APR-128, we shall re-evaluate the data pertaining to the toxicity of the vapors of these compounds and get some estimate of the vapor pressures involved. Shall we hereafter refer to these and other compounds by their new code numbers?

Sincerely yours,

/S/

Sylvan Witherup
Sr. Research Associate

SW/bf

cc: Dr. R. A. Kehoe
Dr. F. F. Heyroth
Dr. L. W. Sanders
Dr. K. V. Kitzmiller

Table 1

The Toxicity of APR-128 When Given Intravenously to Rabbits

(The compound was injected into the marginal vein of the ear as 5 per cent solutions in peanut oil)

Dose of APR-128	Males		Females		Total for Both Sexes		Length of
mg./kg.	D*	T*	D*	T*	D*	T*	Survival
2	0	1	0	1	0	2	
3	0	2	0	1	0	3	
5	2	2	1	2	3	4	10 min. to 18 days
7	2	2	3	4	5	6	1-20 hrs.
10	1	2	3	4	4	6	15 min. to 7 days
16			2	2	2	2	

* D = Number of deaths.
** T = Number of animals that were given the dosage.

Table 2

The Immediate Toxicity of APR-128 When Given Orally to Rats as 2 Per Cent Solutions in Peanut Oil

Dose of APR-128	Males		Females		Total for Both Sexes	
mg./kg.	D*	T*	D*	T*	D*	T*
16			1	3	1	3
24			1	3	1	3
36	0	2	0	3	0	5
55	0	2	2	3	2	5
80	0	2	1	3	1	5
120	0	2	2	3	2	5
180	1	2	2	3	3	5
280	2	2	3	3	5	5
420	2	2			2	2
620	2	2			2	2

Table 3

The Immediate Toxicity of APR-128 When Allowed to Remain in Contact With the Abdominal Skin of Rats

(Solutions containing 2 per cent APR-128 in peanut oil were allowed to remain in contact with the abdominal skin for a continuous period of 6 hours)

Dose of APR-128	Males		Females		Total for Both Sexes		Length of
mg./kg.	D*	T*	D*	T*	D*	T*	Survival
180			0	1	0	1	
280	0	2	0	2	0	4	
420	0	2	1	2	1	4	48 hrs.
620	0	2	0	2	0	4	
940	2	2	2	2	4	4	24-72 hrs.
1400	1	1			1	1	< 24 hrs.

Table 4

The Toxicity of the Vapors of APR-128

(Female rats were individually confined in a glass chamber and supplied with air containing the indicated concentrations of APR-128

Consecutive Minutes of Exposure	Ratio of the Atmospheric Concentration of APR-128 in the Chamber to That in the Air Supplied (Per cent)	Probable Atmospheric Concentration of APR-128 in the Inhalation Chamber (mg./L)			
		T = 24° C. * C = 1.48 mg./L	T = 28° C. * C = 1.71 mg./L	T = 33° C. * C = 2.73 mg./L	T = 37° C. * C = 3.33 mg./L
1	11.3	0.17	0.19	0.31	0.38
5	44.0	0.65	0.75	1.20	1.46
10	68.5	1.01	1.17	1.87	2.28
15	82.3	1.22	1.41	2.25	2.74
20	90.1	1.33	1.54	2.46	3.00
30	96.9	1.43	1.66	2.64	3.23
40	99.0	1.46	1.69	2.70	3.30
60	99.9	1.48	1.71	2.73	
120	99.9+	1.48	1.71		Convulsions in 20 minutes. Died after 37 minutes of exposure.
180	99.99+	1.48		Convulsions in 50 minutes. Died after 88 minutes of exposure.	
360	99.99+	1.48	Convulsions in 120 minutes. Died after 169 minutes of exposure.		
		Convulsions in 5 hrs. Died within a period of 15 hrs. after 6 consecutive hrs. of exposure.			

* T = Temperature at which the air supply was saturated with vapors of APR-128.
* C = Calculated concentration of APR-128 in the air supplied.

Table 5

Comparison of the Toxicity of APR-128 With That of APR-122

Route of Administration	Species of Animals	Sex	Approximate Lethal Dose (mg./kg.)	
			APR-122	APR-128
Intravenous	Rabbits	F	0.7	5.0
		M	2.0	5.0
Oral	Rats	F	10-55	16-80
		M	120.	180.
Percutaneous	Rats	F	280.	420-940
		M	620.	940.
Inhalation	Rats	F	< 0.5 mg./L for 90 min.	< 1.48 mg./L for 6 hrs.