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## Chronic Oral Toxicity to Rats of a Vinyl Chloride-Vinyl Acetate Copolymer

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High molecular weight polymers are generally accepted as safe for food contact, although there is a dearth of published evidence. In particular, no reports of long-time experimental feeding of polyvinyl resins, widely used in food packaging, appear in the literature. In order to fill this gap, a study completed in 1947 is presented.

### METHODS

**Sample.** The sample was then characterized as vinyl resin VYNU.<sup>1</sup> It was a copolymer of 95% vinyl chloride and 5% vinyl acetate, with a molecular weight of 25,000 to 30,000 as determined by the Staudinger method, or 200,000 as measured by osmotic pressure. The resin was produced in the form of particles with a diameter of 0.1  $\mu$  that tended to agglomerate loosely.

**Animal management and observation.** Each of the parental generation group consisted of 12-15 Wistar-strain albino rats of each sex, approximately 6 weeks of age at the first dose. They were housed 4-6, half of each sex, in wire-bottom cages. Ten to 12 offspring of each sex, consisting of the first filial generation, were fed the diets until the end of the study and, as no differences were found from the parental generation rats, both generations were considered together.

For the first 18 months the basic diet consisted of a mixture of 100 parts of ground whole wheat, 5 parts of dried whole milk, and 2 parts of iodized table salt. Wheat then became unavailable to the local miller, and during the last 6 months a commercial ground laboratory chow<sup>2</sup> was utilized. The growth curves of the rats showed no appreciable upset from the shift in basic diets.

One group received the basic diet, one had 1.5% VYNU added, the third had 12% VYNU added, with no attempt made to correct for high nonnutrient content. The respective intakes of VYNU averaged 0.61 and 5.75 g/kg/day.

The observations made during the feeding were (1) tone and behavior of animals, (2) average food consumption, (3) body weight, (4) occurrence of death and infection, (5) red, white, and differential white blood cell counts, and (6) occurrence of pregnancy, number of pups born, and survival and growth of the pups.

At death or sacrifice gross pathology was recorded, and neoplasms were sought. Body length was measured, and livers and kidneys were weighed. Organ weights were calculated as a percentage of body weight.

Adrenal, small intestine, kidney, liver, lung, pancreas, spleen, testis, and neoplasms

<sup>1</sup> Manufactured by a company known at that time as Union Carbide Plastics Division.

<sup>2</sup> Purina Laboratory Chow Meal, Ralston Purina Company, St. Louis, Missouri.

were fixed in formalin, stained with eosin and hematoxylin, and examined histopathologically.

All numerical results were evaluated for statistical significance by Student's *t* test (Fisher, 1938).

#### RESULTS

No abnormalities in body tone or behavior were observed, other than those resulting from chronic murine pneumonia.

Table 1 summarizes the data on survival. The suggestion of a dose-related

TABLE 1  
SURVIVAL OF RATS RECEIVING RESIN VYNU IN THE DIET FOR TWO YEARS

| Dietary level (%) | Rats studied |        | Rats surviving to 365 days of age | Mean age at death <sup>a,b</sup> (days) | Rats surviving to end of study |
|-------------------|--------------|--------|-----------------------------------|-----------------------------------------|--------------------------------|
|                   | Parental     | Filial |                                   |                                         |                                |
| 12                | 28           | 22     | 19                                | 297 ± 152                               | 5                              |
| 1.5               | 27           | 22     | 24                                | 319 ± 156                               | 10                             |
| 0                 | 27           | 24     | 33                                | 344 ± 179                               | 8                              |

<sup>a</sup> Excludes all rats sacrificed for examination.

<sup>b</sup> Mean ± SD.

shortening of life is weakened by the high dispersion of the mean ages at death. Seventy-five rats died of lung infection, and these deaths were distributed equally among the three groups. Seventeen were killed for middle-ear infection, and 4 for other reasons. During the period on the wheat-milk-salt diet the teeth of 6 of the rats, distributed among the three groups, grew continuously without the characteristic rodent attrition, due to the absence of roughage. Three of these were killed when their inability to eat resulted in marked inanition.

Table 2 summarizes the data on dosage, food consumption, and body weight of

TABLE 2  
DIET CONSUMED, DOSAGE, AND BODY WEIGHT OF RATS RECEIVING RESIN VYNU IN THE DIET FOR TWO YEARS

| Dietary level (%) | Mean diet eaten <sup>a</sup> (g. rat/day) | Mean dosage (g. kg/day) | Mean weight of males at 380 days of age <sup>a</sup> (g) | Maximum weight attained by males alive at 380 days of age <sup>a</sup> (g) |
|-------------------|-------------------------------------------|-------------------------|----------------------------------------------------------|----------------------------------------------------------------------------|
| 12                | 11.6 ± 0.3                                | 5.75                    | 375 ± 63                                                 | 412 ± 51                                                                   |
| 1.5               | 10.4 ± 0.2 <sup>b</sup>                   | 0.61                    | 414 ± 88                                                 | 459 ± 116                                                                  |
| 0                 | 11.2 ± 0.3                                | 0                       | 394 ± 69                                                 | 417 ± 79                                                                   |

<sup>a</sup> Mean ± SD.

<sup>b</sup> *P* = 0.04.

males. The body weight of females fluctuated widely because of frequent pregnancy. The suggestion of a lower weight from the high level is weakened by the high standard deviation. Since rats on the low level of VYNU grew as much as did the controls, no importance is attached to their slightly lower diet consumption.

Table 3 summarizes liver and kidney weights, expressed as percentages of body weight, of rats sacrificed after one or two years. At one year, the livers of rats on diets containing 12% VYNU were heavier than those of the controls. They were

TABLE 3  
LIVER AND KIDNEY WEIGHT RATIO DATA ON RATS RECEIVING RESIN  
VYNU IN THE DIET FOR ONE AND FOR TWO YEARS

| Period of feeding | Dietary level (%) | Organ weight as percentage of body weight <sup>a</sup> |                          |
|-------------------|-------------------|--------------------------------------------------------|--------------------------|
|                   |                   | Liver                                                  | Kidney                   |
| 1 Year            | 12                | 4.08 ± 0.43 <sup>b</sup>                               | 0.79 ± 0.18              |
|                   | 1.5               | 3.05 ± 0.37                                            | 0.66 ± 0.05              |
|                   | 0                 | 3.12 ± 0.35                                            | 0.64 ± 0.12              |
| 2 Years           | 12                | 3.06 ± 0.31                                            | 0.59 ± 0.17 <sup>b</sup> |
|                   | 1.5               | 3.05 ± 0.35                                            | 0.66 ± 0.06              |
|                   | 0                 | 3.34 ± 0.43                                            | 0.70 ± 0.10              |

<sup>a</sup> Mean ± SD.

<sup>b</sup>  $P < 0.05$ .

histologically normal, and at two years livers of rats in the same group were numerically but not significantly lighter. Similarly, a slight, but statistically significant, decrease in mean relative kidney weight was seen at two years, but not at one year, with all sections histologically normal. Neither was considered to be a deleterious effect from the inclusion of VYNU in the diet.

Table 4 summarizes the reproduction results and does not suggest any effect.

TABLE 4  
REPRODUCTION OF RATS<sup>a</sup> RECEIVING RESIN VYNU IN THE DIET FOR TWO YEARS

| Dietary level (%) | Females of parental generation |           | Females of F <sub>1</sub> generation |           | Total per female          |                              |
|-------------------|--------------------------------|-----------|--------------------------------------|-----------|---------------------------|------------------------------|
|                   | Total                          | Infertile | Total                                | Infertile | Litters born <sup>b</sup> | Pups born alive <sup>b</sup> |
| 12                | 5                              | 1         | 6                                    | 1         | 6.3 ± 3.5                 | 47.8 ± 28.7                  |
| 1.5               | 5                              | 1         | 4                                    | 0         | 5.5 ± 4.0                 | 45.2 ± 30.4                  |
| 0                 | 10                             | 1         | 6                                    | 1         | 8.4 ± 5.3                 | 51.6 ± 41.0                  |

<sup>a</sup> Alive at 365 days of age.

<sup>b</sup> Mean ± SD.

The tissues of the 38 rats sacrificed for examination after one or two years were histopathologically normal. An infective or traumatic cause of death was clear for all rats dying, and none of their tissues showed any histopathology not directly related to this cause. Careful search of all rats dying or sacrificed revealed only 6 neoplasms, possibly because half of the rats did not survive the lung infection into the second year of feeding. At the 12% level of VYNU there were two neoplasms in the mesentery, at the 1.5% level one uterine neoplasm, and the controls had one in the mesentery and two in the lung.

#### DISCUSSION

This study, completed 20 years ago, differs in many respects from the design one would expect in a current study of the safety of a food-packaging resin. In particular, it would be preferable to add to animal diets only that fraction of the resin which transfers to food packaged in a formulation.

Furthermore, were reproduction considered of sufficient importance to be studied, a separate group of animals would be desirable, with opportunity for mating provided only at estrus.

## SUMMARY

Starting in 1944, albino rats of both sexes caged together were maintained for two years upon diets containing 1.5% and 12% of a vinyl chloride-vinyl acetate copolymer. No effect attributable to the resin was found.

## REFERENCE

FISHER, R. A. (1938). *Statistical Methods for Research Workers*, 7th ed. Oliver & Boyd, Edinburgh and London.