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## SHORT COMMUNICATION

# The Acute Oral Toxicity of Isomeric Monobutylamines in the Adult Male and Female Rat

The Acute Oral Toxicity of Isomeric Monobutylamines in the Adult Male and Female Rat. CHEEVER, K. L., RICHARDS, D. E., AND PLOTNICK, H. B. (1982). *Toxicol. Appl. Pharmacol.* **63,** 150–152. The acute oral $LD_{50}$ values of *n*-butylamine, isobutylamine, *sec.*-butylamine, and *tert.*-butylamine were detemined in both male and female Sprague–Dawley CD rats. Signs of toxicity observed after single oral doses of the monobutylamines included sedation, ataxia, nasal discharge, gasping, and salivation followed by convulsions and death at the higher dose levels. Gross pathological examination of animals that died after the monobutylamine treatment revealed pulmonary edema. The $LD_{50}$ values for the monobutylamines were calculated by the probit method of D. J. Finney (1971, *Probit Analysis*, 3rd ed., Cambridge Univ. Press, Cambridge). No significant sex-related differences were noted. The 14-day, po single-dose $LD_{50}$ values (mg/kg body wt) were: *n*-butylamine, male 365.4, female 382.7; isobutylamine, male, 224.4, female, 231.8; *sec.*-butylamine, male, 157.5, female, 146.8; and *tert.*-butylamine, male, 82.3, female, 78.1.

The four isomeric monobutylamines are finding increasing use in the manufacture of such diverse products as textiles, plastics, dyestuffs, corrosion inhibitors, lubricating oil additives, antioxidants, fungicides, herbicides, rubber chemicals, and emulsifying agents. Despite this widespread use, available information on the toxicity of these compounds is fragmentary. For *n*-butylamine and *sec.*-butylamine the oral toxicity has been considered in the rat, albeit with different or unspecified sexes. But no such toxicity data for isobutylamine or *tert.*-butylamine have been reported.

As an estimate of the single-dose po toxicity of "commercial grade" *n*-butylamine, Smyth and Carpenter (1944) derived, from a range-finding test, an "R.F. $LD_{50}$" of 500 mg/kg body wt for 90- to 120-g male rats. Although the $LD_{50}$ derived from the range-finding test was considered by these researchers to be "an extremely rough approximation," the value has been cited in numerous publications as an expression of the oral toxicity of *n*-butylamine in the rat. In addition to the value reported by Smyth and Carpenter, Sutton (1963) listed in a review an $LD_{50}$ range of 200 to 400 mg/kg body wt for the po toxicity of *n*-butylamine in rats of unspecified sex or strain.

The po $LD_{50}$ values for *sec.*-butylamine in adult and newborn Harlan Wistar rats were listed by Goldenthal (1971) in a compilation of $LD_{50}$ values from various sources. In 42- to 49-day-old females, the $LD_{50}$ was reported as $380 \pm 20$ mg/kg body wt, whereas, in rats less than 2 days old, the $LD_{50}$ was reported as $350 \pm 30$ mg/kg body wt.

This paper reports the acute oral toxicity of the four isomeric monobutylamines in male and female rats. The $LD_{50}$ values were obtained under the same test conditions and, thus, are directly comparable.

## METHODS

The test chemicals, *n*-butylamine (>99%), isobutylamine (>98%), *sec.*-butylamine (>99%), and *tert.*-butylamine (99.5%), were purchased from Tridom Chemical Inc., Hauppauge, New York.[1]

Male and female weanling Sprague–Dawley CD rats of the same age were obtained from the Charles River Breeding Laboratories, Wilmington, Massachusetts. These animals were housed two per cage and were acclimated to laboratory conditions for 2 weeks prior to initiation of the experiment. Laboratory temperatures ranged from 22 to 26°C, and the relative humidity ranged from 22 to 49%. A 12-hr light–dark schedule

[1] Mention of company or product names is not to be considered an endorsement by the National Institute for Occupational Safety and Health.

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was maintained with the light cycle beginning at 7:00 AM. Except for an 18-hr period immediately prior to treatment, the animals were provided with Rodent Laboratory Chow (Ralston Purina Co., St. Louis, Mo.). Tap water was available *ad libitum*.

In a range-finding study, rats were treated in groups of two males and two females with various amounts of the test compounds. From the resulting mortality data, a range of doses for each of the monobutylamines was established. Solutions of the monobutylamines were then prepared in corn oil such that doses of 100, 200, 300, 400, 500, and 600 mg/kg body wt for *n*-butylamine, isobutylamine, and *sec.*-butylamine, and doses of 30, 40, 50, 70, 100, and 200 mg/kg body wt for *tert.*-butylamine could be administered in a constant 4-ml volume.

Upon initiation of the toxicity experiment, the rats were starved overnight, weighed (males, 194.7 ± 20.5 g; females, 156 ± 16.8 g), and randomly assigned to 24 dosage groups, each group consisting of 10 male and 10 female rats. The specified doses of each monobutylamine were administered, by gavage, to all rats within the corresponding dosage groups. These animals were observed for signs of toxicity or mortality during the subsequent 14-day period, and those that died during this period were subjected to gross pathological examination. $LD_{50}$ values for each monobutylamine were calculated for both males and females from the mortality in the several groups by the probit method of Finney (1971). Data for male and females were compared statistically for each compound by the $\chi^2$ contingency table analysis (Snedecor and Cochran, 1967).

## RESULTS AND DISCUSSION

As determined in this study, *tert.*-butylamine was the most toxic of the monobutylamines, followed by *sec.*-butylamine and isobutylamine with *n*-butylamine being the least toxic. There was a four-fold difference between $LD_{50}$ values of the most and least toxic compounds, and no statistically significant sex-related differences were found. The single-dose $LD_{50}$ values for these compounds are listed in Table 1. Signs of toxicity, common to all of the monobutylamines, included sedation, ataxia, nasal discharge, gasping, salivation, and, at higher doses, convulsions and death. At the dose levels tested, death generally occurred within 1 to 3 hr after administration of the amine. Animals which survived the 14-day period appeared normal and were not further examined. Gross pathological examination of animals that died following treatment showed

TABLE 1

ACUTE ORAL TOXICITY OF MONOBUTYLAMINE ISOMERS IN FASTED RATS[a]

| Compound | Sex | $LD_{50}$ (mg/kg body wt) (95% confidence limits)[b] | Slope (±SD)[b] |
|---|---|---|---|
| *n*-Butylamine | M | 365.7 (283.6–475.8) | 3.80 (±0.99) |
| | F | 382.4 (278.1–490.5) | 2.71 (±0.81) |
| | M and F[c] | 371.8 (307.8–458.4) | 3.17 (±0.62) |
| Isobutylamine | M | 224.4 (136.3–303.1) | 2.71 (±0.73) |
| | F | 231.8 (106.1–345.9) | 2.00 (±0.68) |
| | M and F | 227.9 (161.5–289.5) | 2.34 (±0.49) |
| *sec.*-Butylamine | M | 157.5 (35.1–242.8) | 1.89 (±0.67) |
| | F | 146.8 (12.4–239.3) | 1.67 (±0.66) |
| | M and F | 152.4 (69.3–214.8) | 1.78 (±0.47) |
| *tert.*-Butylamine | M | 82.3 (57.0–144.5) | 2.25 (±0.69) |
| | F | 78.1 (60.8–107.9) | 3.47 (±0.83) |
| | M and F | 79.9 (65.0–102.9) | 2.78 (±0.53) |

[a] Test compounds administered to 10 male and 10 female rats at six dose levels in 4 ml/kg body wt corn oil.
[b] Calculated using the probit method of Finney (1971).
[c] Male and female rat mortality data were not statistically different. Combined $LD_{50}$ values were calculated for these groups using the probit method of Finney (1971).

pulmonary edema, an effect observed for certain other aliphatic amines by Hanzlik (1923) and Hine *et al.* (1960).

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