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Author	竹内, 雅也(Takeuchi, Masaya) 前川, 昭彦(Maekawa, Akihiko) 多田, 敬三(Tada, Keizo) 小田嶋, 成和(Odashima, Shigeyoshi)
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Leukemios and Vaginal Tumors in Female Donryu Rats by Continuous Administration of 1-Butyl-3, 3-dimethyl-1-nitrosourea in the Drinking Water*

MASAYA TAKEUCHI, AKIHIKO MAEKAWA, KEIZO TADA, and SHIGEYOSHI ODASHIMA

竹内雅也, 前川昭彦, 多田敬三, 小田嶋成和 (国立衛生試験場)

1-Butyl-3,3-dimethyl-1-nitrosourea (DiM-BNU) was synthesized by nitrosation of 1-butyl-3, 3-dimethylurea, prepared by reaction of butyl isocyanate with liquid dimethylamine in toluene, with an aqueous solution of sodium nitrite and 25% sulfuric acid at 0-3° C, purified by column-chromatography on silica gel with petroleum benzine-ethyl acetate (5:2, vol/vol), and identified by UV, IR, NMR, and element analysis.

Three groups of five-week-old female Donryu rats, each of which consisted of 36, were maintained on the base diet CE-2 and tap water until they were 11 weeks old, and thereafter, were continuously given a solution of DiM-BNU as their drinking water (400 ppm for A, 200 ppm for B, and 100 ppm for C daily).

Of the 100 rats that survived at least 122 experimental days, 64 developed leukemia (26 of 33 in A, 79%, 23 of 31 in B, 74%, and 15 of 36 in C, 42%), and 38 had vaginal tumors (6 in A, 13 in B, and 19 in C), 28 mammary tumors (5 in A, 9 in B, and 14 in C), and 15 ear-duct tumors (7 in A, 4 in B, and 4 in C). A very low incidence of tumors was also detected in the forestomach, intestine, thyroid, liver, brain, and lung. Total number of rats with tumors were 90 (90%), and mean survival time was shortest in A (212 ± 42 days) and longest in C (317 ± 58 days).

There was a dose-effect relationship for leukemia and other tumors. A higher dose of DiM-BNU generally resulted in higher incidence of leukemia and ear-duct tumors, and a lower dose induced more tumors in the vagina and mammary glands.

The cytologic types of leukemia induced were classified into three major types—myelocytic, (12 of 26 in A, 14 of 23 in B, 14 of 15 in C), myeloblastic (9 in A, 4 in B, 0 in C), and erythroblastic (3 in A, 1 in B, 0 in C). Of all leukemic rats, 12 was noted with chloro-leukemia, 10 of which were myelocytic.

Incidence of leukemia in this study was lower than that produced by 1-ethyl-1-nitrosourea and 1-butyl-1-nitrosourea, but similar to that caused by 1-propyl-1-nitrosourea. It was ascertained that the carcinogenic action of DiM-BNU was similar to that of other 1-alkyl-1-nitrosoureas such as the above described chemicals, except that DiM-BNU produced vaginal tumors. The results concerning with the type of leukemia coincide with those previously reported, too.

Spontaneous vaginal tumors in rats are rare. No vaginal tumors in rats have been

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reported as a result of oral administration of any chemicals, although some have been induced by other methods, such as local application of various chemicals by Boyland et al. [Brit. J. Cancer, **15**, 252 (1961)] . It may be also noted that the incidence of vaginal tumors in this study was extremely high compared with reports by Alexandrov [Nature, **222**, 1064 (1969)] and Herrold [J. Pathol., **92**, 35 (1966)], although all tumors were papillomas.