The single LD₉₀ doses of TBP given orally were 1.24 g/kg (male mice), 0.9 (female mice), 1.39 (male rats) and 1.53 (female rats). No marked difference of LD₉₀ values was observed among three administration routes. Hematological observations revealed no marked changes except BUN values which increased 6-48 hours after the administration. Pathologically, degeneration of the tubules was the major finding in an acute intoxication.

Seven consecutive daily intubation of TBP for rats in doses of 0.14 and 0.20 (0.98 and 1.40 g/kg in total) resulted in marked increments of relative weights of liver and kidneys in accompany with an increase of BUN value and tubular degeneration. The daily intubation of 0.13 and 0.46 g/kg of TBP for one month caused in rats a marked depression of body weight gain and lethal cases by 20 and 40%, respectively. Tubular damage was also a major change.

Three months feeding experiments in doses of 0, 0.05, 0.2 and 1.0% of TBP for mice and rats revealed dose-dependent depression of body weight gain, increments of liver, kidney and testis weight, and decrease in uterus weight. No significant changes were observed in hematological analysis except an increment of BUN value both in mice and rats administrated with high level of TBP. Diarrhea was observed during these acute and subacute experiments.

These toxicological surveys on TBP revealed that TBP is not so high toxic chemical but caused kidney damage in experimental animals.

SACCHARIN-INDUCED HYPERPLASIA OF THE RAT URINARY BLADDER:
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Epithelial hyperplasia of the urinary bladder caused by sodium saccharin in male F344 rats was studied by light microscopy, scanning electron microscopy (SEM), and autoradiography. The rats were given sodium saccharin mixed in a powder diet at a dose of 5.0% by weight and killed at several intervals for up to 18 weeks. By light microscopy, vacuolar degeneration of the epithelial cells was observed at 3 weeks and simple hyperplasia was present by 9 weeks through 18 weeks. Papillary or nodular hyperplasia was not observed. By SEM the bladders had focal, small, irregularly shaped, flat mucosal lesions after 5 weeks. The cells in the areas had luminal surfaces covered with rop, rounded microridges and short, uniform microvilli. After 9 weeks, small, irregularly shaped foci with a slight degree of elevation of cells, giving the mucosa a cobblestone appearance, were observed. Most of the cells in these foci were with short, uniform microvilli and with ropy, rounded microridges. In addition, small, round cells having pleomorphic microvilli on their luminal surface were observed in these foci. Hyperplastic foci were observed in all rats fed sodium saccharin after each of weeks 9, 12, 15 and 18, and they did not appear to increase in number or extent during
these 9 weeks.

Autoradiographs indicated that increased thymidine uptake in the mucosa was present compared to the control group. The labelled cells were clustered in multiple, small foci. Most of the labelled nuclei were observed in basal cells. Superficial cells were rarely labelled.

These data demonstrate that sodium saccharin induces a hyperplastic response in the rat bladder, the target organ for its promoting activity.

ULTRASTRUCTURAL STUDY OF THE ACUTE CHANGES
OF URINARY BLADDER EPITHELIUM IN RATS
INDUCED BY A HIGH DOSE LEVEL OF BBN:
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N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) is a potent urinary bladder carcinogen in rats and mice.

Relatively few studies have looked at the acute changes of urinary bladder epithelium in rats induced by high dose levels of BBN.

Male Fischer rats, 8 weeks-old, were divided into 2 groups. The experimental group received 900 mg/kg BBN (1/2 LD<sub>50</sub>) for 3 days intragastrically, and the control group was given just vehicle alone.

Animals were sacrificed 1, 2, 3, 4, and 6 weeks after the last administration of BBN, and on histopathologic and ultrastructural examinations were perfomed on the urinary bladder and other major organs.

Light microscopid findings: at 1 week, after BBN gavage, transitional epithelium was generally in three cell layers, almost the same as with normal bladder; at 2 weeks, the epithelium was increased 6 to 8 cell layers and this simple hyperplasia was slightly reduced at 6 weeks after treatment, but still showed 5 cell layers of bladder epithelium multifocally.

Electron microscopic findings: the bladder epithelium of control animals was composed of three cell layers, superficial, intermediate, and basal cell layers; at 1 week, the nucleus of superficial and intermediate cells, showed nucleolar segregation, a fibrillary type of nuclear body and fenestration of the endothelium of the capillary vessels below the basement membrane; at 2 weeks, segregation and compression of the nucleolus and several types of nuclear bodies were seen to be increased and these changes persisted until 6 weeks. The control group did not show nucleolar segregation, nuclear bodies or capillary fenestration throughout the experimental period.

The results of this study revealed that nucleolar segregation, nuclear bodies and fenestration of capillaries could be seen within 1 week, instead of 4 to 6 weeks as is usual following oral administration of BBN.

Furthermore, these changes, were found usually in preneoplastic cells, with papil-