# LONG-TERM EFFECTS OF VARIOUS IODINE AND FLUORINE DOSES ON THE THYROID AND FLUOROSIS IN MICE

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**Objective.** To elucidate the participation of the independent and combined long term effect of various concentrations of iodine and fluorine on the pathogenesis of goiter and fluorosis in mice.

**Methods.** Nine drinking water supplies with different iodine and fluorine content were prepared by combination of potassium iodate and sodium fluoride solutions in bidistilled water. The concentrations of iodide were: 1. iodine deficiency (ID): 0.0; 2. iodine normal (IN): 20.0; 3. iodine excess (IE) 2500.0 μg/l; and these of fluoride were: 1. fluoride deficiency (FD) 0.0; 2. fluoride normal 0.6; 3. fluoride excess (FE), 30.0 mg/l. A total of 288 Kunmim mice was divided into 9 groups consisting of 32 animals each and each group, in addition to basal diet, received one of following iodide/fluoride mixtures: ID+FD, ID+FN, ID+FE, IN+FD, IN+FN, IN+FE, IE+FD, IE+FN, IE+FE. By such manner, one half of the animals of each group was treated for 100 days and the other half for 150 days.

**Results.** It was found that ID only and IE only could both induce the goiter. FE induced dental fluorosis and increased fluorine content in the bone. In addition, fluorine also affected the thyroid changes induced by ID or IE. After 100 days of treatment, fluorine showed some stimulatory effect on the thyroid in ID conditions and inhibitory effect in IE conditions. After 150 days, however, the effects of fluorine on the thyroid reversed as compared with that of 100 days. On the other hand, difference of iodide intake could also increase the toxic effects of FE on the incisors and bones. The rate and degree of the incisor fluorosis, the fluorine contents in the bone were significantly higher in the ID+FE group than those in the IN+FE and IE+FE groups.

**Conclusions.** Both iodine deficiency and excess induced goiter as well as other functional and histopathological changes in the mouse thyroid. Excessive fluorine caused fluorosis of incisors and limb bones. In addition, iodine and fluorine do have mutually interacting effects on both goiter and fluorosis in the experimental mice.

**Key words:** Iodine – Fluorine -Various doses – Goiter- Fluorosis – Mice

The distribution of iodine and fluorine in the environment, especially in the underground water, is usually similar. Yet, endemic goiter (iodine deficiency disorder – IDD) and fluorosis seldom occur in the same area or in the same population at the same time (Feng 1981; Lin 1984). However, even the excess of iodine in water and food has been shown to induce goiter both in normal and in endemic fluorosis coastal and inland areas in China and possible effects of fluorine on goiter were noticed (Ma et al. 1982; Zhu et al. 1984; Yu et al. 1988; Yang et al. 1994). In addition to fluorine present in underground waters, even the fluorine pollution from burning coal appears to be another important pathogenic factor of the endemic fluorosis in China (Li 1982). Thus, there is no doubt that some rural IDD areas in China may be equally affected by fluorine pollution from coal burning. Actually, even the fluorosis caused by excess fluorine in drinking water was also reported in one area of IDD (Ren et al. 1989).

So far, the observations on the exact effects of fluorine on the thyroid have been quite controversial (Day 1972; Bobek et al. 1976; Hara 1980; Baum et al. 1981; Siebenhurer et al. 1984; Yu et al. 1985; Zhao et al. 1988, 1992; Yang et al. 1994). One of possible reasons for this is thought to be the different iodine intake interfering with the effect of fluorine on thyroid (Demole 1970; Buergi et al. 1984). Thus, it appears reasonable to study the effects of iodine and fluorine on the thyroid under various combinations of iodine and fluorine intake as well as the iodine influence on fluorosis induced by fluorine. It was found that the response to iodine and fluorine excess in mouse resembles that found in man (Zhu et al. 1988; Zhao et al. 1992). Thus, the aim of this study was to elucidate both the independent and combining effects of those two elements on the pathogenesis of goiter and fluorosis.

## Materials and Methods

**Experimental animals and treatment.** A total of 288 male Kunmin mice weighing 13 to 15 g was purchased from the Experimental Animal Institute, Chinese Medical Academy. After adaptation, they were randomly divided into nine groups of 32 animals each (from which sick animals that suffered a infectious disease after long-term study were excluded for experimental observation) and were allowed free access to basal chow and drinking water with different amounts of iodine and fluorine (see bellow). The iodine and fluorine solutions were prepared by the addition potassium iodate ($KIO_3$) and/or sodium fluoride (NaF) into bidistilled water. Three concentrations of iodine (iodine deficiency [ID] – 0.0; iodine normal [IN] – 20.0 and iodine excess [IE] – 2500 μg/l and fluorine (fluorine deficiency [FD] – 0.0, fluorine normal [FN] – 0.6 and fluorine excess [FE] – 30.0 mg/l) were used. Special low iodine and low fluorine chow was prepared by the Experimental Animal Institute of Hebei Medical University with the use of grains from an IDD area in China: corn 38 %, wheat 33 %, millet grain 20 %, soybean 7 %, yeast 1 %, soybean oil 0.5 %, sodium chloride 0.5 %, egg 1 %. The body weight of all animals was estimated in two week intervals. Ethical introduction contained in "Guidelines on the Handling and Training of Laboratory Animals" were observed.

**Evaluation of fluorosis.** Two weeks after the beginning of experiment, incisor fluorosis was checked weekly and classified using the criteria shown in Tab. 1.

**Radioiodine uptake.** After 100 and 150 days of treatment the carrier containing $^{131}I$ was injected i.p. in a dose of 0.2 μCi/100 g. The animals were sacrificed 6 h later, the blood was withdrawn and the thyroids were dissected. The $^{131}I$ uptake by the thyroid was estimated routinely.

**Histopathological observations.** The thyroids were weighed and fixed in 10 % formol, embedded in paraffin and the sections of 5 μm thickness were stained with hematoxyline and eosine. The follicular diameter and follicular cell height were measured in the light microscope. According to histological findings the thyroid was classified as hyperplastic goiter (HG), colloid goiter (CG), normal or almost normal thyroid (NT), intermediate status between NT and HG (abbreviated as NH) or between NT and CG (abbreviated as NC).

**Estimation of serum triiodothyronine ($T_3$) and thyroxine ($T_4$).** The sera obtained by centrifugation were stored at -30 °C until assayed. Serum triiodothyronine and thyroxine were estimated by commercial kits purchased from the General Navy Hospital (Beijing, China).

**Estimation of fluorine in bones, fluorine and iodine in drinking water and chow.** The selective fluoride electrode method was used for the estimation of fluoride in the ashes of the limb bones (recovery 84.9 to 110.76 %), drinking water and in the mouse chows (recovery 89.9 to 105.27 %). The mouse chow has been burned at 550 °C for 3 h, and iodine in the ashes has been extracted with bidistilled water. The content of iodine in the water extracted from the ashes and the drinking water for the nine groups of mice was analyzed by the Ce/As method (recovery 86.81 – 96.75 %).

**Statistical evaluation.** ANOVA and ONE WAY in a statistical software named SPSS (Norusis 1995) and the "Cross Product Different Method (CPD)" (Wang 1981) were used to analyze the qualitative and ranked data, respectively. With these methods either the effect of iodine or fluorine alone or the combined effects of iodine and fluorine can be analyzed. The differences between every pair of two groups were also analyzed after the significant difference among the whole 9 groups has been found with the methods described above.

**Table 1**
Criterion of Incisor fluorosis

| | Normal | Questionable | Mild | Moderate | Severe |
|---|---|---|---|---|---|
| Glossy | Good | Good | Not good | Bad | Bad |
| Color | Deep yellow of upper incisor or Egg white color of lower incisor | Light yellow of upper incisor and white lower incisor | Deep white of of lower incisor | Deep white of lower incisor | Deep white of lower incisor |
| Vitrifiction | semivitriform | Slight Aberration of translucency | Opaque | Opaque | Opaque |
| Chalky white area | No | No | Flecks or spots | Areas | Areas |
| Pit or break | No | No | No | No | Have |

**Table 2**
Changes in Body Weight of Mice after 100 and 150 Days (g)

| Fluorine Level | Iodine level | | | Significant for iodine[b] |
|---|---|---|---|---|
| | ID | IN | IE | |
| FD | 31.5±6.76 (11)[a]<br>49.7±2.91 (12) | 35.0±4.15 (14)<br>51.9±5.13 (14) | 34.1±5.36 (16)<br>49.9±4.98 (9) | P>0.05<br>P>0.05 |
| FN | 32.2±6.20 (11)<br>50.7±4.71 (9) | 40.7±6.12 (13)<br>56.0±1.41 (8) | 39.3±5.45 (7)<br>55.4±5.31 (14) | P>0.01<br>P>0.05 |
| FE | 34.1±3.91 (12)<br>51.5±4.12 (14) | 38.5±3.92 (16)<br>53.5±2.46 (12) | 39.5±4.95 (12)<br>53.7±3.83 (15) | P>0.01<br>P>0.05 |
| Significant for fluorine | P>0.05<br>P>0.05 | P<0.05<br>P>0.05 | P<0.05<br>P<0.05 | |

[a]: Represent the mean ± SD for mice weighed after 100 days (upper lines) and 150 days (lower lines), the number in brackets represent number of animals
[b]: Significant for iodine represents statistically significant P value between the ID, IN and IE within a same fluorine level, and significant for fluorine represents statistically significant P value between FD, FN, FE within a same iodine level

**Table 3**
Changes in thyroid weight (mg) and relative weight (mg/100g wt) after 100 days

| Fluorine Level | Iodine level | | | Significant for iodine[b] |
|---|---|---|---|---|
| | ID | IN | IE | |
| FD | 2.05±1.26 (11)[a]<br>10.34±2.72 | 3.01±0.97 (14)<br>9.63±2.46 | 4.51±0.84 (16)<br>13.80±4.52 | P<0.01<br>P<0.05 |
| FN | 3.62±0.92 (11)<br>11.41±2.88 | 2.97±1.19 (14)<br>8.04±2.42 | 4.14±1.32 (14)<br>10.55±2.98 | P>0.05<br>P<0.05 |
| FE | 4.38±1.25 (12)<br>12.08±3.60 | 3.12±1.08 (15)<br>8.72±2.01 | 3.57±1.17 (12)<br>9.22±3.53 | P<0.05<br>P<0.01 |
| Significant for fluorine | P<0.01<br>P>0.05 | P>0.05<br>P>0.05 | P>0.05<br>P<0.05 | |

[a]: Represent the mean ± SD of the thyroid weight (upper lines) and relative thyroid weight (lower lines), the number in brackets represent number of mice
[b]: Significant for iodine represents statistically significant P value between the ID, IN and IE within a same fluorine level, and significant for fluorine represents statistically significant P value between FD, FN, FE within a same iodine level

**Table 4**
Changes in the $^{131}I$ uptake ratios of mice (%)

| Fluorine Level | Iodine level | | | Significant for iodine[b] |
|---|---|---|---|---|
| | ID | IN | IE | |
| FD | 21.39±1.40 (10)[a] | 19.34±0.97 (14) | 1.21±0.04 (16) | <0.01 |
| | 64.83±1.55 (10) | 37.68±3.61 (14) | 1.02±0.10 (10) | <0.01 |
| FN | 37.04±1.12 (11) | 11.58±0.56 (14) | 3.42±0.27 (11) | <0.01 |
| | 70.87±3.58 (11) | 14.61±2.04 (11) | 1.17±0.14 (14) | <0.01 |
| FE | 39.18±0.96 (12) | 7.13±1.39 (16) | 1.49±0.27 (11) | <0.01 |
| | 46.39±1.93 (12) | 17.40±1.20 (12) | 0.86±0.04 (13) | <0.01 |
| Significant for fluorine | <0.01 | <0.01 | <0.01 | |
| | <0.05 | <0.01 | >0.05 | |

[a]: The numbers in the table represent the means ± SD of the $^{131}I$ uptake ratios after 100 days (upper lines) and after 150 days (lower lines). The number in brackets represent number of mice.
[b]: Significant for iodine represents statistically significant P value between the ID, IN and IE within a same fluorine level, and significant for fluorine represents statistically significant P value between FD, FN, FE within a same iodine level.

**Table 5**
Incisor fluorosis in the FE groups

| Observation Time (day) | Group (number of mice) | Questionable | Incisor Fluorosis | | | |
|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | rate (%) |
| 30 | ID+FE (14) | 0 | 0 | 2 | 11 | 92.9 |
| | IN+FE (12) | 2 | 2 | 3 | 2 | 58.3** |
| | IE+FE (15) | 5 | 6 | 2 | 0 | 53.3** |
| 60 | ID+FE (14) | 0 | 0 | 6 | 8 | 100.0 |
| | IN+FE (12) | 1 | 1 | 9 | 0 | 83.3** |
| | IE+FE (15) | 0 | 4 | 4 | 7 | 100.0 |
| 90 | ID+FE (14) | 0 | 0 | 6 | 8 | 100.0 |
| | IN+FE (12) | 4 | 3 | 2 | 1 | 50.0** |
| | IE+FE (15) | 1 | 5 | 3 | 5 | 86.7** |
| 150 | ID+FE (14) | 0 | 3 | 7 | 4 | 100.0 |
| | IN+FE (12) | 0 | 8 | 4 | 0 | 100.0* |
| | IE+FE (15) | 2 | 12 | 1 | 0 | 86.7** |

*, **: P<0.95, and P<0.01 for the comparison of incisor fluorosis rate and degree with the ID+FE group

## Results

**Body weight.** As shown in Tab. 2, the body weight in the IN or IE groups was higher (in some cases significantly) than that in ID groups. The same was true for FE conditions at 100 days, while no significant differences in body weight could be found between the groups with different iodine intake at day 150, suggesting that the excess of fluorine can minimize the weight difference between the mice with different iodine intake.

**Absolute and relative thyroid weight.** Both the absolute and relative thyroid weight was increased in ID and also in IE groups at 100 (Tab. 3) and 150 days (not shown) irrespective of the level of fluorine intake. At 100 days in ID groups the absolute thyroid weight increased with fluorine intake (P<0.01; Tab. 3), but no difference in relative thyroid weight was found, since the body weight of mice increased simultaneously (Tab. 2). However, under IE conditions at 100 days the relative thyroid weight decreased with increasing fluorine intake (P<0.05; Tab. 3). Af-

**Table 6**
Changes of fluorine content of the limb bones (ppm)

| Fluorine Level | Iodine level | | | Significant for iodine[b] |
|---|---|---|---|---|
| | ID | IN | IE | |
| FD | 743.3±162.4 (11)[a] | 316.3± 76.9 (14) | 569.9±121.6 (15) | <0.01 |
| | 435.8± 50.8 (12) | 642.1±144.9 (13) | 901.3±268.4 (9) | <0.01 |
| FN | 379.7± 49.4 (11) | 362.6± 50.4 (14) | 545.8± 99.1 (7) | <0.01 |
| | 704.2±132.5 (9) | 1156.0±128.1 (8) | 737.1± 62.9 (14) | <0.01 |
| FE | 2563.59±252.6 (12) | 2104.3±263.5 (9) | 2382.2±632.6 (9) | <0.01 |
| | 2877.4 ±217.0 (12) | 1826.9± 81.5 (12) | 2141.6±205.1 (15) | <0.01 |
| Significant for fluorine | <0.01 | <0.01 | <0.01 | |
| | <0.01 | <0.01 | <0.01 | |

[a]: The numbers in the table represent the means ± SD fluorine content in the limb bones after 100 days (upper lines) and after 150 days (lower lines). The number in brackets represent number of mice.
[b]: Significant for iodine represents statistically significant P value between the ID, IN and IE within a same fluorine level, and significant for fluorine represents statistically P value between FD, FN, FE within a same iodine level.

ter 150 days the absolute and relative thyroid weight was significantly increased in ID and IE groups irrespective of fluorine intake (not shown).

**Histopathological characteristics of the thyroid.** The incidence of hyperplastic goiter in ID groups (18 – 66 % at 100 days and 81 – 100 % at 150 days) and that of colloid goiter in IE groups (27 – 85 % at 100 days and 55 – 92 % at 150 days) was significantly higher than that in IN groups (7 – 26 % at 100 days and 6 – 14 % at 150 days). This shows that either iodine deficiency or excess could induce goiter in mice. In addition, the increase of goiter incidence with time shows that the longer the treatment with deficient iodine and excess iodine, the higher the goiter rate.

Moreover, under ID conditions after 100 days the incidence of goiter increased with increasing intake of fluorine, being 18 % in ID+FD group, 40 % in ID+FN group and 66 % in ID+FE group. In contrast, however, under IE conditions after 100 days the incidence of colloid goiter decreased with increased fluorine intake, being 55 % in IE+FD group and 92 % in both IE+FN and IE+FE group. Similar interrelations were found also in absolute and relative thyroid weight at day 100 (Tab. 3). However, a majority of these changes either disappeared or were inverted as the treatment time reached 150 days.

Histometrical parameters showed that under ID conditions the follicular cell height and the ratio of follicular cell height/follicular diameter increased, while the follicular diameter decreased. Under the IE condition, the follicular cell height and the ratio of follicular cell height/follicular diameter decreased, while the follicular diameter increased. As for the combining effects of the two elements, it was found that the follicular cell height under the conditions of ID and EF could increase at day 100 and decrease at day 150.

**Serum $T_3$ and $T_4$ levels.** In general, after 100 days the level of $T_3$ (mean±S.D.) in ID+FD (0.49±0.27 ng/ml), ID+FN (0.49±0.25 ng/ml), IE+FD (0.42±0.23 ng/ml), IE+FN (0.48±0.24 ng/ml) and IE+FE (0.47±0.24 ng/ml) groups was significantly lower than that in all IN groups (IN+FD 1.02±0.50 ng/ml, IN+FN 0.95±0.09 ng/ml and IN+FE 0.90±0.45 ng/ml). Excessive fluorine in iodine deficient (ID+FE) group resulted in increased $T_3$ level (1.52±0.33 ng/ml).

After 100 days the level of $T_4$ was decreased by iodine deficiency, the levels in ID+FD (45.2±14.39 ng/ml) and ID+FN (46.2±11.21 ng/ml) groups being significantly lower than these in IN and IE groups at FD and FN level (68.2±12.80 ng/ml and 89.7±14.68 ng/ml) with the exception of these at FE level (116.9±15.13 ng/ml in ID+FE, 101.6±18.36 ng/ml in IN+FE and 98.8±8.20 ng/ml in IE+FE). After 150 days the decrease in all ID groups was much more remarkable irrespectively of fluorine intake (the average values were 5.0 to 9.6 μg/ml, while the levels in all IN and IE groups were about a half of these shown above for the appropriate groups after 100 days.

**Radioiodine uptake by thyroid.** As shown in Tab. 4, after both 100 and 150 days the iodine intake was the most significant factor influencing the $^{131}I$ uptake which was inversely related to the level of iodine. However, the fluorine excess (FE) significantly inhibited the radioiodine uptake in ID and IN groups, while such effect was not observed at IE level.

**Incisor fluorosis and fluorine content in bones.** No incisor fluorosis was observed in FD and FN groups, while it was found as early as 2 weeks after FE treatment. Tab. 5 further shows that the severity of fluorosis was higher in ID groups and not increased with time from 30 to 150 days. As shown in Tab. 6, the content of fluorine in the limb bones dramatically increased with the intake of fluorine and that in all ID and IE groups it was higher than that in FN groups.

## Discussion

It is well known that iodine deficiency can influence the development of animals and human beings as well (Hetzel et al. 1989). Such interrelation also appeared in this experiment since the body weight in all iodine deficient groups was decreased, while this was not the case under excessive iodine intake. This is in accordance with the results of our previous findings (Tan et al. 1990; Zhao et al. 1992).

Although it has been expected that the uptake of radioiodine by thyroid will be inversely related to the iodine intake, the effect of fluorine was unpredictable. In the past decades, several authors showed that increasing fluorine intake inhibited the thyroid uptake of radioiodine in different animals as well as human beings (Galletti et al. 1958; Takada 1958; Zhang 1982; Sidora et al. 1983; Yu et al. 1985; Bachinskii et al. 1985). However, even the contradictory findings were reported. Thus, Clay et al. (1987) fed heifers with 30 and 50 ppm of fluoride in dry matter for one year and did not find any changes in radioiodine uptake. McLaren et al. (1976) reported similar results obtained in rats and human beings. Yanagisawa (1984) found that the uptake was inhibited by fluorine when a small dose of radioiodine was given, while this was not the case after relatively larger dose. In our experiment, a relatively large dose of radioiodine (0.2 μCi/100 g wt) was used. Under the ID conditions, fluorine in normal and excessive level increased thyroid radioiodine uptake after 100 days, but as the treatment with the same fluorine doses reached 150 days, the uptake was inhibited. Under the IN and IE conditions, excessive fluorine tended to show reducing effect on the radioiodine uptake. Thus, it seems that the effect of fluorine on radioiodine uptake varied with the changes in fluorine concentration and exposure time as well as with these of iodine.

In this study excessive iodine intake increased the serum $T_4$ level, but such effects did not appear after 150 days of treatment. At the same time, however, excessive iodine decreased serum $T_3$ level. These results showed that excessive iodine intake may affect the thyroid function which is in accordance with the findings in other studies (Zhu et al. 1984; Zhu et al. 1988; Zhao et al 1990). Our previous study revealed that after the excessive iodine intake the thyroid secretory function might change from time to time, even in the same population or in same animals (Zhao et al. 1992). It was also reported that the thyroids in infant and neonate period were more sensitive to the influence of excess iodine than these in adults. Based on the above results, we suggest that the thyroid function of these who are taking excessive iodine, especially that in pregnant women and infants, should be strictly monitored namely by the estimation of TSH, $T_4$ and $T_3$ levels.

It is generally believed that fluorine does not influence either thyroid function or structure at the amount (about 1 ppm in water) used to prevent the dental caries (Buergi et al. 1984). However, if fluorine intake is extremely high such as in an endemic fluorosis area or in the cases when fluoride treatment is used, the secretion of $T_4$ and $T_3$ from the thyroid could be influenced. Yu et al. (1985) reported a decreased serum $T_4$ level and increased TSH level in the residents of endemic fluorosis area where the urinary iodine level (162.7±48.7 μg/24 h) suggested adequate iodine intake. In an animal experiment, Yu et al. (1985) found that 50 ppm fluoride in water could reduce serum $T_4$ and $T_3$ in rats. Bachinskii et al. (1985) compared the serum TSH and thyroid hormone levels in the area with high fluorine concentration in water (122 ± 5 μmol/l, i.e. about 2.3 ppm) and a control area (52 ± 5 μmol/l, i.e. about 1.0 ppm) and found that the healthy people who lived in the high fluorine area tended to take up more iodine and had decreased $T_3$ and increased TSH levels. Decreased $T_3$ and/or $T_4$ levels were also observed in animal exper-

iments (Guan et al. 1988; Hara 1980). McLaren et al. (1976) stated that the thyroid function may be influenced by the fluorine intake higher than 5 mg/day. However, Hara (1980) found that 1, 5, 10, 50, 100 and 200 ppm fluoride in water could decrease the serum $T_3$, and 1 ppm fluoride increase the $T_4$ in rats fed with standard chow (F- 34.5 ppm). When the rats were fed with low fluoride chow (F- 0.31 ppm), the decrease of the $T_3$ by fluoride in water disappeared, but the increase of $T_4$ by 1 ppm fluoride in water was similar to that found in the rats fed with standard chow. The results of this experiment showed that excessive fluorine intake increased serum $T_3$ and $T_4$ levels of iodine treated mice, especially in iodine deficiency conditions. We cannot offer any plausible explanation for the discrepancies between our results and those of other reports. One of our assumptions is that the mouse we used might differ in this respect from the rat or other animals used by others (Yu et al. 1985; Guan et al. 1988; Hara 1980). Another explanation may be that the influence of fluorine on thyroid function varies with the time of exposure, chow fed and doses of fluoride chosen.

The changes in the thyroid weight and histopathological features in experimental mice under the ID condition were the same as those reported elsewhere (Zhu et al. 1988). Although the thyroid weight increased in all ID groups, histological changes in FE treated mice showed obvious hyperplasia at day 100 as compared with FD and NF groups. Considering the fact that fluorine excess, especially in ID conditions, could increase serum $T_3$ and $T_4$, it is reasonable to suggest that fluorine could stimulate the thyroid directly or indirectly within 100 days in this experiment. After 150 days, however, although the $T_4$ level in ID+FE group was still higher, the thyroid weight and follicular cell height decreased and the follicular diameter increased, suggesting that the stimulatory effect of fluorine on the thyroid had been decreased.

The excessive iodine intake could increase thyroid weight and induce colloid goiter under different fluorine intake (FD, FN and FE), the effect of such excessive iodine being the same as that of iodine deficiency, since it induced goiter irrespective of the low or high intake of fluorine. In addition, fluorine deficiency affected the increase of relative thyroid weight, while excessive fluorine decreased the incidence of goiter caused by iodine excess.

Although the disorders induced by abnormal iodine and fluorine intake can occur simultaneously in the same human population, no report has been found about the combined influence of iodine and fluorine on dental and skeletal fluorosis. The results of this experiment showed that iodine deficiency increased the incisor fluorosis incidence and severity of the injuries caused by excessive fluorine. At the same time, both ID and IE could increase the fluorine content in the limb bones. Since, under FD conditions, significant differences in bone fluorine content under different iodine conditions were also observed, these apparently indicate that iodine intake does influence the dental and skeletal fluorosis.

In conclusion, the results suggest that both iodine deficiency and excess could induce goiter as well as other functional and histopathological changes in thyroid. Excessive fluorine could cause fluorosis of incisors and limb bones. In addition, iodine and fluorine do have mutually interacting effects on both goiter and fluorosis in the experimental mice.

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