

**EXPERIMENTAL PHARMACOLOGICAL
RESEARCHES REGARDING THE INFLUENCE OF
SODIUM FLUORIDE IN ALLOPATHIC AND
HOMEOPATHIC DOSES ON CENTRAL NERVOUS
SYSTEM'S PERFORMANCES. A CORRELATION
BETWEEN BEHAVIORAL RESPONSE IN CLASSIC
MAZE TEST AND MORPHOLOGICAL ASPECTS OF
CEREBRAL CORTEX**

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Abstract

The influence of fluorine administration on central nervous system's (CNS) performances in female mice treated during gestation with two distinct doses of sodium fluoride (NaF): 0.25 mg and 0.50 mg. The research extended also to offspring (generation 1 – F1), treated with NaF in allopathic (0.25 and 0.50 mg), homeopathic (7CH) or with the association between the two types (allopathic and homeopathic) of doses. CNS performance modification was also assessed in the second generation offspring (F2), in which fluorine was exclusively taken from ascendant generations. Evaluation of CNS activity was performed by determining clearing time in classic maze (CM) at several time intervals (roughly 21 days between determinations). Experimental results showed that, in young offspring (1 – F1) from ascendants treated with the same substance, CNS performances in investigative capacity are influenced depending on dose, gender and age. Similar effect was recorded for homeopathic remedy 7CH for which the influence on CNS performance is strongly correlated to the stage of physical development of offspring and to doses of NaF administered to ascendants.

The results of pharmacological tests correlate strongly to modifications noted during anatomical pathology examination of cerebral cortex.

Rezumat

Am urmărit influența administrării fluorului asupra performanțelor sistemului nervos central (SNC) la șoareci femele tratate în perioada gestației cu două doze diferite de NaF: 0,25 mg și 0,5 mg. Cercetarea a fost extinsă și la descendenții acestora (generația 1 – F1), tratați cu NaF în doze alopate (0,25 mg și 0,5 mg), homeopate: 7CH NaF, sau cu asocierea dintre cele două tipuri de tratament: alopate și homeopate. Modificarea

performanțelor centrale a fost evaluată și la generația a doua (F2), la care fluorul a provenit exclusiv prin preluare de la generațiile anterioare.

Evaluarea activității centrale s-a realizat prin determinarea timpului de parcurgere al labirintului clasic (LC), la mai multe intervale de timp (în jur de 21 zile între două determinări). Rezultatele experimentale au evidențiat faptul că fluorura de sodiu administrată la animale tinere (1 – F1) provenite din ascendenți tratați anterior cu aceeași substanță, influențează performanțele centrale privind capacitatea de investigare a acestora dependent de doză, sex și vârstă. Aceleași efect au fost evidențiate și pentru remediul homeopat 7CH, la care influența asupra performanțelor centrale este strâns corelată cu stadiul dezvoltării fizice al animalelor și cu dozele de NaF administrate anterior ascendenților.

Rezultatele testelor farmacologice sunt în strânsă corelație cu modificările evidențiate în cadrul examenului anatomopatologic al cortexului cerebral.

Keywords: sodium fluoride, classic maze, behavior, brain

Introduction

Fluorine is one of the substances used in prophylaxis in medicine and it is administered [4] involuntary, by water or food fluoridation, or voluntary, by medical prescription, daily from birth to adulthood. The researchers began to study the effects of fluorine on living cells - plants, animals and humans. From the point of view of the human body it was discovered that there are alterations of cerebrovascular integrity [11, 16] or modifications at the synaptic level [9, 17]. At the same time, numerous researches on laboratory animals were performed, for example researches on behavior [1] or neurotoxicity [6, 13] or brain modifications, yielded by before and after birth administration of fluoride [2], sometimes on generations that succeeded one another [3]. Using as template studies on human behavior [8], studies of toxicology in animals [10, 15] and the principles of homeopathy [7], it was authors' intention to identify a correlation between the fluoride, administered in allopathic or homeopathic doses [12] or as association of the two types of treatments and the behavioral changes along with the structural modifications of the brain.

Materials and Methods

Materials: male and female white mice, NMRI strain; NaF solution 0,25 ‰ ; NaF solution 0,5 ‰ ; NaF homeopathic remedy, 7CH dilution; hematoxylin-eosine (HE) solution;

Methods

Male and female laboratory mice NMRI strain were studied.

Females were housed together with males for a week for reproductive purposes. After mating, gestating females were divided in 3 groups (16 animals/group) and were treated as follows: group I – 0.25 mg NaF, 0.25 ‰

solution p.o.; group II – 0.5 mg NaF, 0.5 %₀ solution p.o.; group III – distilled water 0.1 mL/10 g-bw p.o.;

Administration of substances started from day 8 after mating, main duration 14 ± 3 days (until litter deliverance). No substances were administered further to females once litter delivered.

From the litters 14 groups were formed (generation 1 – noted F1) treated according to table I description.

Upon sexual maturity, two pairs of each F1 group were randomly chosen to breed next. This generation did not receive treatment and was noted as generation 2 (F2).

Clearing time (s) determination in classic maze

Mice were submitted to cognitive test consisting in classic maze (CM), noting clearing time (seconds) in which each animal passes through. For the initial females (that delivered the first generation offspring) 3 evaluations were performed in CM at roughly 21 days interval. For the F1 groups two evaluations were performed at similar interval while for the F2 groups a single evaluation was observed, 21 days after groups were designated.

Table I

Experimental protocol of research groups forming

Females						
Control females			0.25 mg NaF females		0.5 mg NaF females	
Generation 1 (F1)						
Control Group female	Group 1A female 7CH NaF _{0.5 mg}	Group 1B female 7CH+0.5 mg NaF	Group 1C female 0.5 mg NaF	Group 2D female 7CH NaF _{0.5 mg}	Group 2E female 7CH + 0.25 mg NaF	Group 2F female 0.25 mg NaF
Control Group male	Group 1A male 7CH – NaF _{0.5 mg}	Group 1B male 7CH + 0.5 mg NaF	Group 1C male 0.5 mg Na F	Group 2D male 7CH - NaF _{0.5 mg}	Group 2E male 7 CH + 0.25 mg NaF	Group 2F male 0.25 mg NaF
Generation 2 (F2)						
Control Group female	Group 1A female 7CH NaF _{0.5 mg}	Group 1B female 7CH+0.5 mg NaF	Group 1C female 0.5 mg NaF	Group 2D female 7CH NaF _{0.5 mg}	Group 2E female 7CH + 0.25 mg NaF	Group 2F female 0.25 mg NaF
Control Group male	Group 1A male 7CH – NaF _{0.5 mg}	Group 1B male 7CH + 0.5 mg NaF	Group 1C male 0.5 mg Na F	Group 2D male 7CH - NaF _{0.5 mg}	Group 2E male 7 CH + 0.25 mg NaF	Group 2F male 0.25 mg NaF

Anatomic pathology examination

Randomized mice were chosen for the anatomical pathology study from every group, both males and females. At the end of the experiment, animals were euthanized by cervical dislocation. The brain was prelevated and preserved in 10% formol, then prepared for optic microscopy by HE coloration.

All procedures have been observing bioethical regulations for scientific research in experimental animals according to Directive 86/609/EEC from November 24th, 1986.

Statistical analysis

Statistic calculation used GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com). Normal distribution (Dn) was tested using D'Agostino & Pearson test. Statistical evaluation has employed the tests: *t Student* (for normal distribution); *Mann-Whitney* (for abnormal distribution).

Experimental results from CM testing

Table II and figure 1 contain CM clearing time alterations, comparatively to control group, for female groups that delivered first generation offspring. Table III and figures 2 – 5 contain CM clearing time alterations, comparatively to control group and to groups treated exclusively with NaF, for male and female groups from the F1 generation. Statistical significance resulted from *t Student* test as distribution inside each group was normal. Figures 6 - 7 contain CM clearing time alterations for the second generation groups, males and females, for which fluorine is exclusively inherited from previous generations.

Table II

Alterations ($\Delta\%$) of CM clearing time (s) for female groups that delivered the first generation litters. Statistical significance of results: *t Student*.

Parameter/ Group	Female group – Assesment 1			Female group – Assesment 2			Female group – Assesment 3		
	Group I- Control	Group II- NaF 0.25mg	Group III- NaF 0.5mg	Group I- Control	Group II- NaF 0.25mg	Group III- NaF 0.5mg	Group I- Control	Group II- NaF 0.25mg	Group III- NaF 0.5mg
M $\pm$ SD	11.40 $\pm$ 0.07071	10.32 $\pm$ 0.1111	10.46 $\pm$ 0.1140	11.37 $\pm$ 0.05060	10.22 $\pm$ 0.1215	10.39 $\pm$ 0.1427	11.31 $\pm$ 0.233	10.16 $\pm$ 0.4544	10.31 $\pm$ 0.4919
Effect % /control		-9.47	-8.98		-10.11	-8.61		-10.16	-8.84
p/control		0.0001 ***	0.0001 ***		0.0001 ***	0.0001 ***		0.0001 ***	0.0001 ***

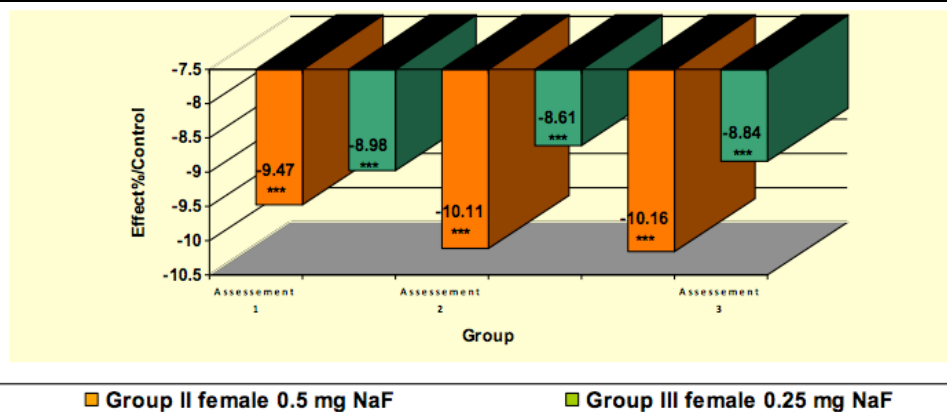


Figure 1

Alterations ($\Delta\%$) of CM clearing time for gestating female groups treated with NaF: 0.25 mg and 0.5 mg, against control group

Table III
Alterations ($\Delta\%$) of CM clearing time (s) for first generation offspring (F1). Statistical significance of results: t Student.

GROUP	Control		Group 1A -7CH - NaF _{0.5} mg		Group 1B -7CH + 0.5 mg NaF		Group 1C - 0.50 mg NaF		Group 2D -7CH - NaF _{0.25} mg		Group 2E -7CH + 0.25 mg NaF		Group 2F - 0.25 mg NaF	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Parameter														
M $\pm$ SD	142.3 $\pm$ 8.612	114.2 $\pm$ 6.322	147.2 $\pm$ 9.783	190.9 $\pm$ 6.457	179.8 $\pm$ 8.094	215.9 $\pm$ 9.184	148.4 $\pm$ 3.082	108.8 $\pm$ 6.375	180.8 $\pm$ 5.170	157.4 $\pm$ 4.564	279.6 $\pm$ 10.27	77.12 $\pm$ 5.940	83.58 $\pm$ 4.376	134.0 $\pm$ 5.977
$\Delta\%$ / control		-19.74	3.42	67.16	26.35	89.05	4.28	-4.72	27.05	37.82	96.48	-32.46	-41.26	17.33
p/ control		0.0001 ***	ns	0.0001 ***	0.0001 ***	0.0001 ***	ns	ns	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***
p/NaF			ns	0.0001* **	0.0001 ***	0.0001 ***			0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***		
$\Delta\%$ /NaF			-0.80	39.05	21.15	98.43			115.36	17.46	234.52	-42.44		
Evaluation 2														
Parameter														
M $\pm$ SD	143.9 6.384	59.22 $\pm$ 7.402	110.8 $\pm$ 8.450	209.6 $\pm$ 9.836	106.9 $\pm$ 2.955	87.95 $\pm$ 3.194	76.57 $\pm$ 5.666	129.6 $\pm$ 4.313	104.1 $\pm$ 6.845	75.37 $\pm$ 3.868	107.74 $\pm$ 9.4140	88.58 $\pm$ 3.9480	281.05 $\pm$ 6.5453	170.95 $\pm$ 8.1231
$\Delta\%$ / control		-58.84	-23.00	253.93	-25.71	48.51	-46.78	118.8	-27.65	27.27	-25.12	49.57	95.30	188.66
p/ control		0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***
p/NaF			0.0001 ***	0.0001 ***	0.0001 ***	0.0001 ***			0.0001* **	0.0001 ***	ns	0.0001 ***		
$\Delta\%$ /NaF			44.70	61.71	39.61	32.13			-62.29	-55.91	-61.66	-48.18		

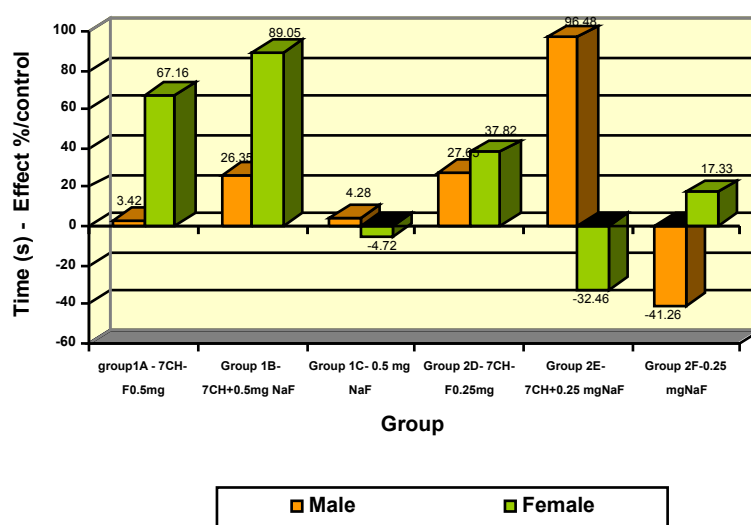


Figure 2

Alterations ($\Delta\%$) of CM clearing time (s), against control group, for males and female of first generation (F1) – **Evaluation 1**

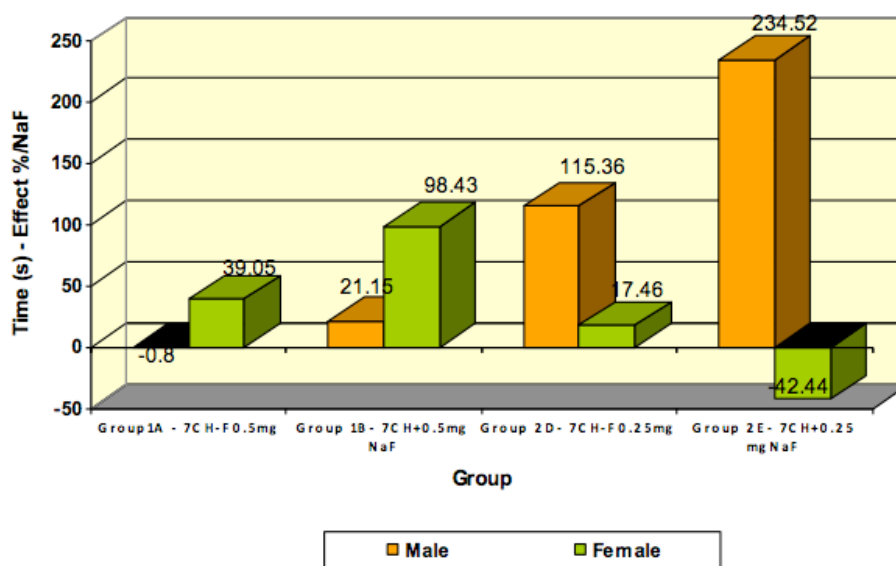
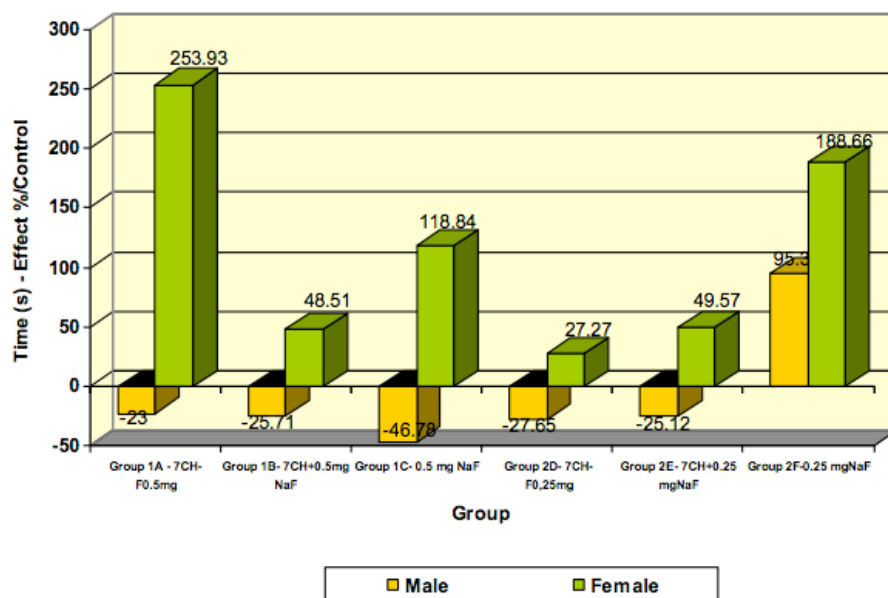
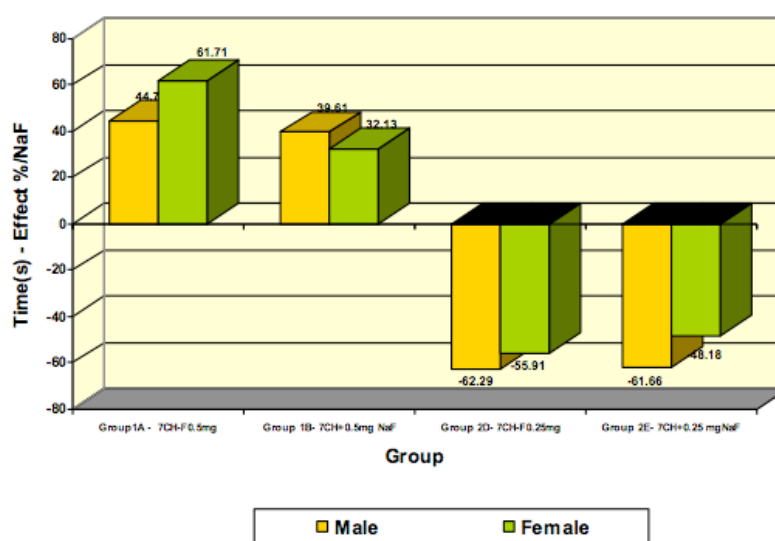


Figure 3

Alterations ($\Delta\%$) of CM clearing time, against group treated with allopathic NaF (0.50 mg; 0.25 mg), for males and females of first generation (F1) – **Evaluation 1**

**Figure 4**

Alterations ($\Delta\%$) of CM clearing time against control group for males and females of first generation (F1) – **Evaluation 2**

**Figure 5**

Alterations ($\Delta\%$) of CM clearing time, against group treated with allopathic NaF (0.50 mg; 0.25 mg), for males and females of first generation (F1) – **Evaluation 2**

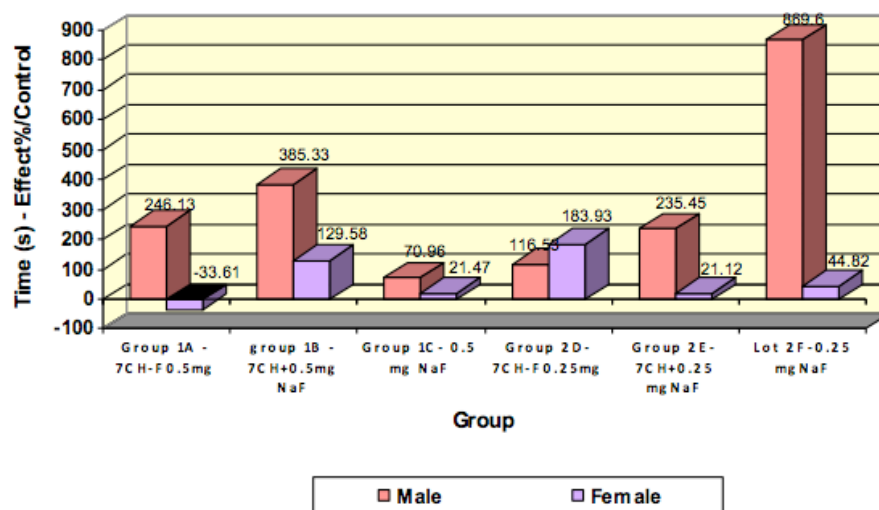


Figure 6

Alterations ($\Delta\%$) of CM clearing time against control group for males and females of second generation (F2) – **Evaluation 3**

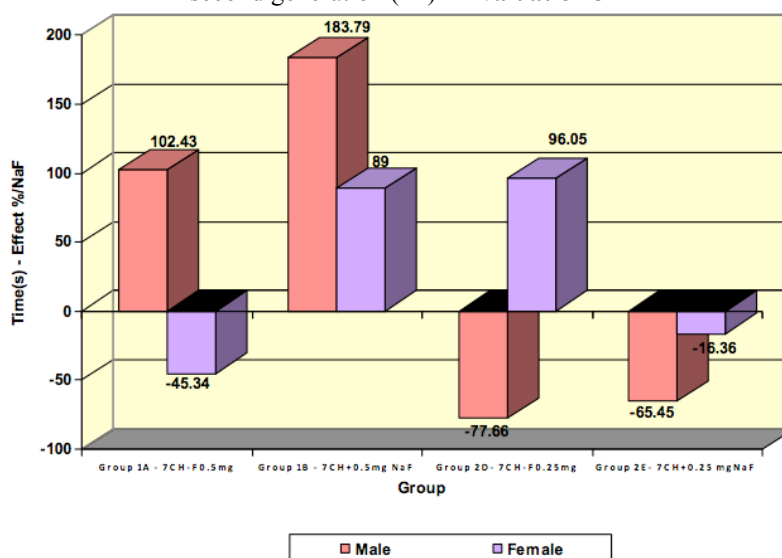
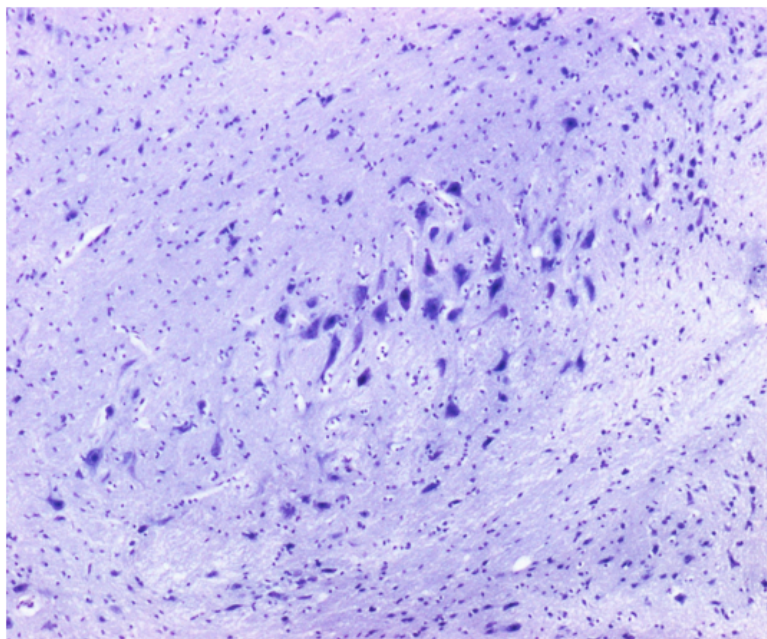


Figure 7

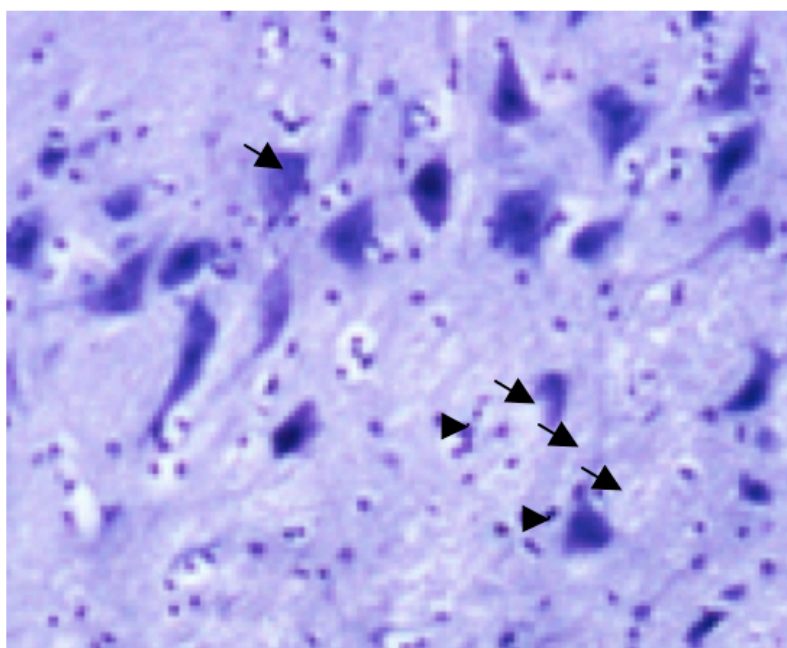
Alterations ($\Delta\%$) of CM clearing time, against group treated with allopathic NaF (0.50 mg; 0.25 mg), for males and females of second generation (F2) - **Evaluation 3**

Experimental results from anatomical pathology examination of the brain

Table IV organizes the alterations of analyzed cerebral structures from experimentally tested animal groups while the figures no. 8 – 17 show microscopical corresponding images.

**Figure 8**

Necrosis of the pyramidal neurons in the cortex (HE 100X)

**Figure 9**

Neuronal necrosis in the cerebral cortex. Glial satellitosis in the pyramidal neurons (head arrow), tigroid changes (tail arrow) (HE 400X)

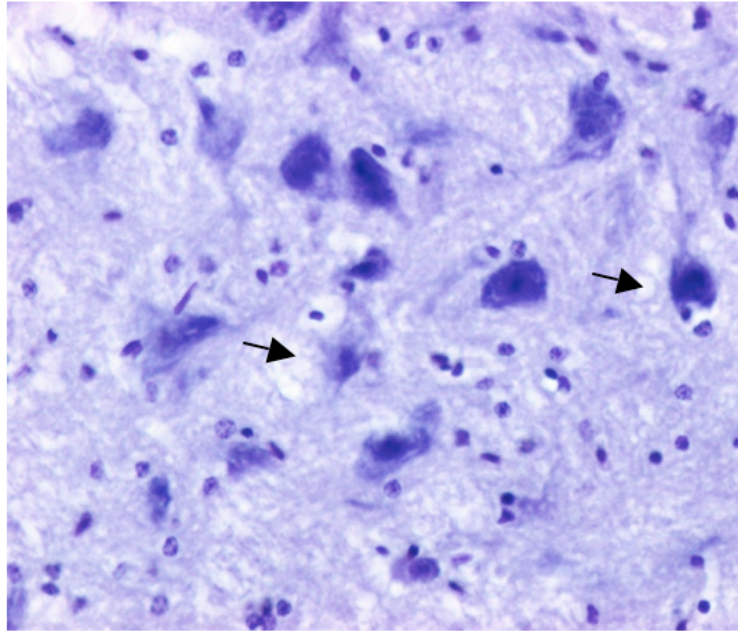


Figure 10
Vacuolar degeneration of the cortex (arrow) (HE 400X)

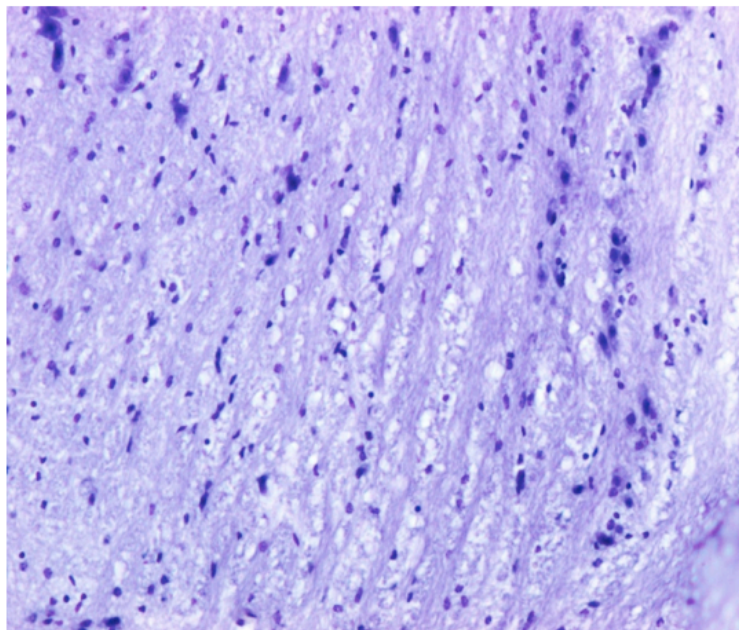
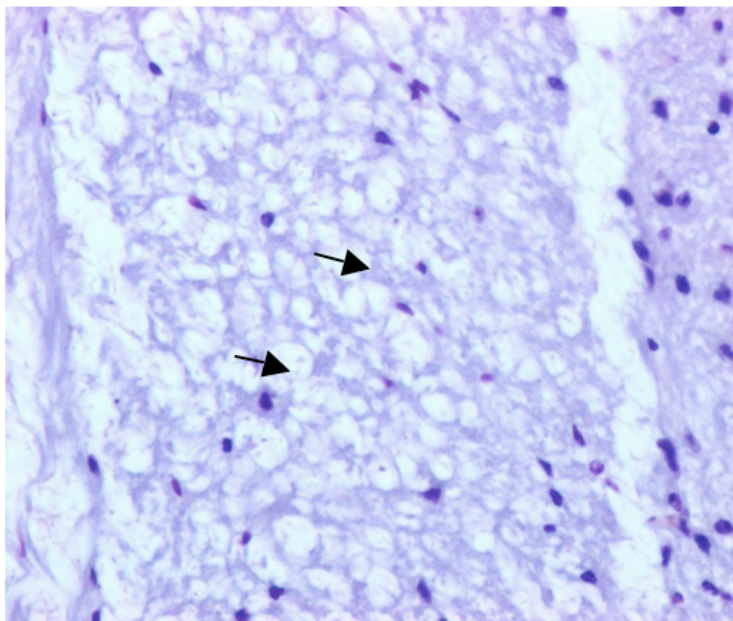
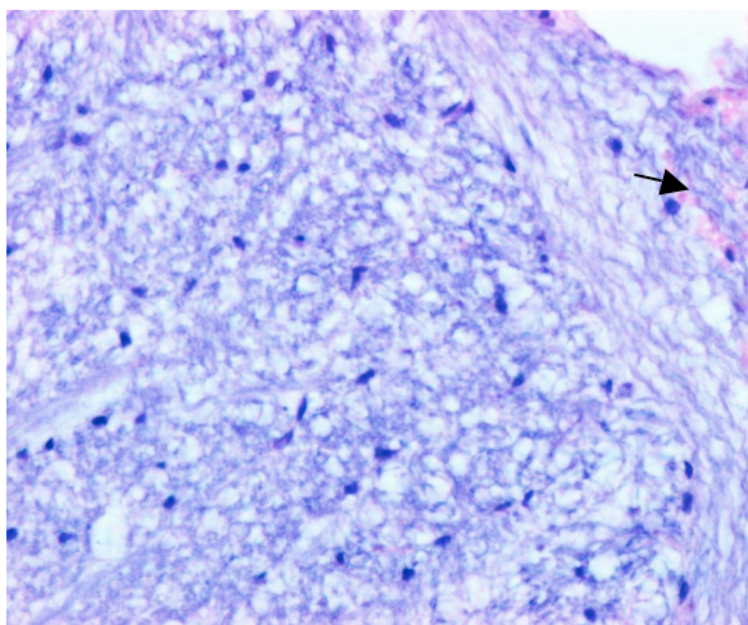


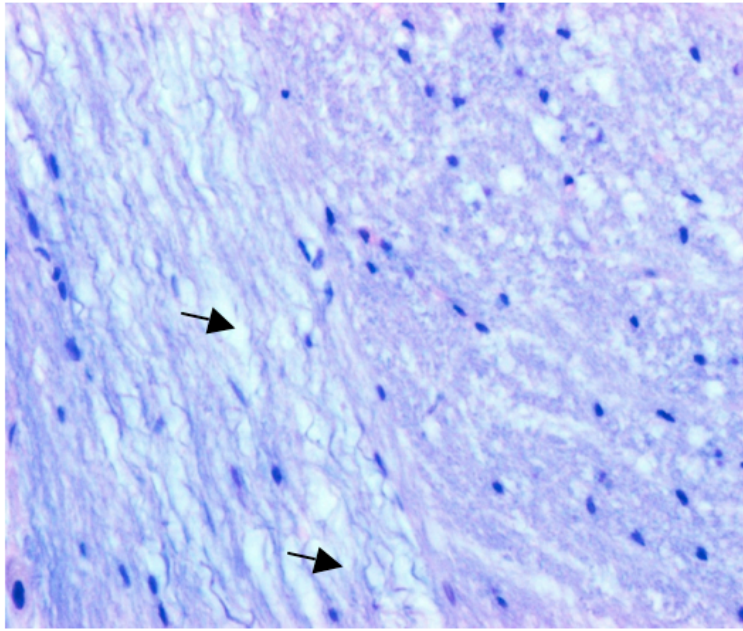
Figure 11
Vacuolar degeneration into the cortex (HE 200X)

**Figure 12**

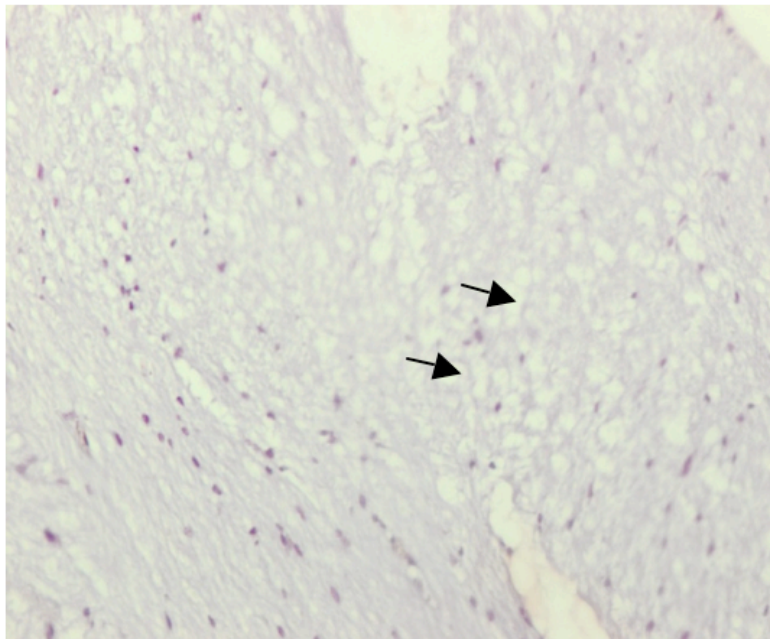
Vacuolar degeneration into the cortex (arrow) (HE 400X)

**Figure 13**

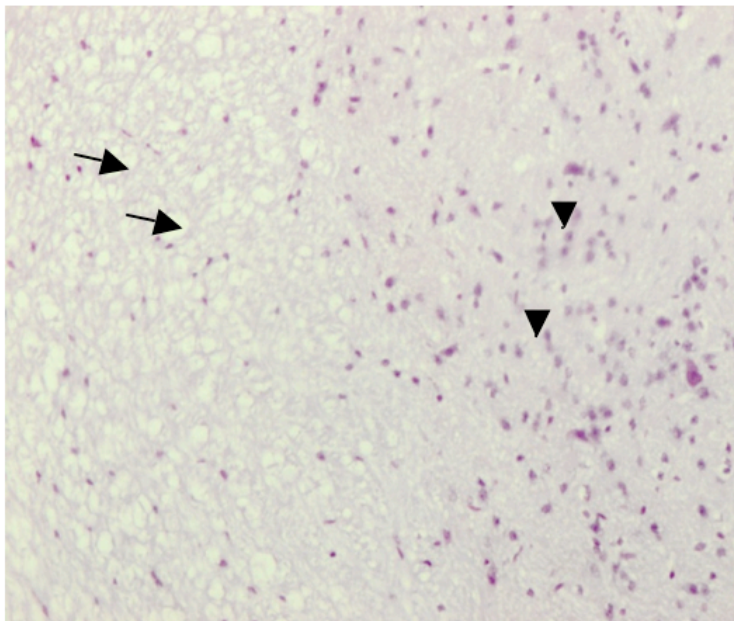
Vacuolar degeneration into the cortex and hyperemia in capillaries (arrow) (HE 400X)

**Figure 14**

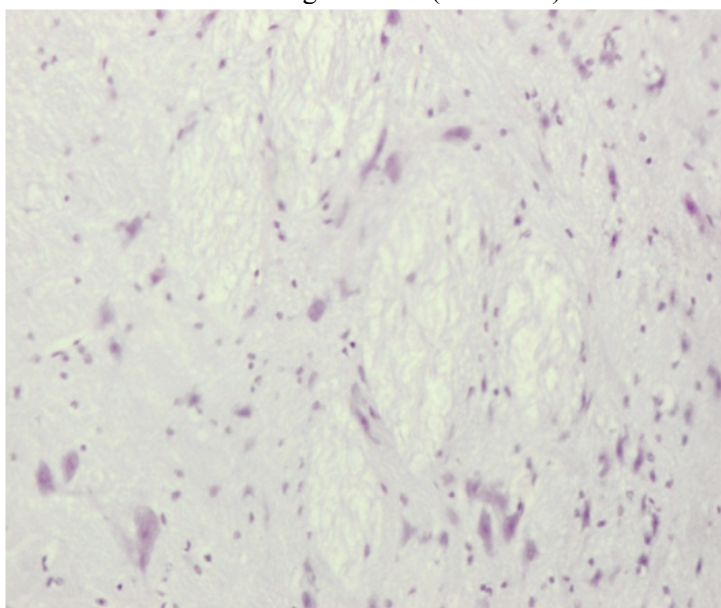
Vacuolar degeneration of cerebral tissue-cortex (arrow) (HE 200X)

**Figure 15**

Vacuolar degeneration of cerebral tissue- cortex (arrow) (HE 200X)

**Figure 16**

Vacuolar degeneration of cerebral tissue-cortex (tail arrow) and found increased number of glial cells. (HE 200X)

**Figure 17**

Vacuolar degeneration of cerebral tissue- cortex and found increased number of glial cells.

Table IV

Anatomo-pathological alterations of cerebral structures

Group	Group 1A –CH – F _{0.5} mg		Group 1B –7CH + 0.5 mg NaF		Group 1C – 0.50 mg NaF	
	Male	Female	Male	Female	Male	Female
Observation	- necrosis of neurons in the cerebral cortex; - satellitosis of neuroglial cells	- satellitosis of glial cells of the cortex;	- necrosis of pyramidal neurons in the cerebral cortex	- necrosis of neurons in the cerebral cortex; - vacuolar degeneration of the cortex	- neuronal necrosis ; - satellitosis of glial cells in the cortex;	- vacuolar degeneration of the cortex; - neuronal necrosis;
Group	Group 2D – 7CH – F _{0.25} mg		Group 2E – 7CH + 0.25 mg NaF		Group 2F – 0.25 mg NaF	
	Male	Female	Male	Female	Male	Female
Observation	-neuronal necrosis; -satellitosis of glial cells in the cortex;	- neuronal necrosis;	- neuronal necrosis; - satellitosis of glial cells in the cortex;	- discreet neuronal necrosis;	- necrosis of pyramidal neurons in the cortex;	- discreet neuronal necrosis in cortex;

Results and Discussion

For the females that delivered the first generation offspring, administration of NaF (0.25; 0.5 mg) induced a stimulation of the cognitive activity of clearing the CM, highly significant statistically ($p < 0.0001$), as observed in table I and figure 1.

The decrease in the maze clearing time was not dose-dependant, so for the 0.5 mg NaF dose this parameter decreases during the three evaluations by a percentage greater than 8.6 (table I). For the 0.25 mg NaF, the percentage reduction of animals' clearing time varies between 9.47 and 10.16 during evaluations 1, 2 and 3.

Evaluation 1- generation F1

For the male and female groups of the first generation a statistically significant (table II) difference can be observed regarding the CM clearing time in both evaluations (1, 2). Thus, for female groups a smaller time of clearing the maze is recorded: - 19,74% (evaluation 1), respectively - 58,84% (evaluation 2), against male corresponding groups.

Administration of 0.5 mg NaF did not influenced significantly maze clearing time for the male and female groups of the first generation (F1) (table II), against control group.

Administration of 0.25 mg NaF induced a statistically significant stimulation of CNS cognitive activity ($p < 0.0001$) for the male group (Group 2F – 0.25 mg NaF), expressed in reduction of maze clearing time by 41,26%

against control group. For the female group the same dose of NaF induced an increase of the time (table no. 2; figure no. 2) by 17,33% ($p < 0.0001$).

Administration of NaF 7CH homeopathic remedy in offspring from females treated with allopathic 0.5 – 0.25 mg NaF (group 1A – Homeopathic 7CH – $F_{0.5}$ mg; group 2D – Homeopathic 7CH – $F_{0.25}$ mg) induced an increase of maze clearing time (table no. 2; figure no. 3), both for males and also for females from generation 1, compared to control group or with groups treated exclusively with NaF.

Treatment association between 7CH homeopathic remedy with the two distinct allopathic doses of NaF induced similar effects of decreased CNS activity in treated animals. The sole exception registered in this experiment was for females: group 2E – Homeopathic 7CH + 0.25 mg NaF, in which the association of the two types of doses (allopathic and homeopathic) has induced a statistically significant decrease in maze clearing time against control group (-32.46%; $p < 0.0001$) and also against the group treated exclusively with NaF (-42.44%; $p < 0.0001$).

Evaluation 2 - generation F1

Administration of NaF in 0.5 mg dose in first generation offsprings has induced different effects on classic maze clearing time, as follows:

- for females, an increase in maze clearing time was registered (table II, figure 4), against control group. The decrease in CNS activity is also supported by the results of morpho-pathological alterations in the cerebral structures (figures no. 12 - 17);
- for males, a decrease of the clearing time was registered (-46.78%; $p < 0.0001$), against control group.

In the case of 0.25 mg NaF administration, a depressed CNS activity for both group genders, expressed as statistically significant increase in maze clearing time (table no. 2; figure 4). These results correlate with morpho-pathological alteration observed in cerebral structures (table III).

Administration of 7CH homeopathic remedy in offspring of females treated with 0.25 mg or 0.5 mg NaF have induced an increase of maze clearing time that was statistically significant against control group (table II; figure 4). Depressed CNS activity highlighted in this test was in correlation with morpho-pathological alterations induced in females (table III; figures 8 - 11). For males, the clearing time decreased against control group.

Within the results of the evaluation 2, it can be observed that 7CH homeopathic remedy, administered alone or in association with 0.5 mg NaF, induces (against the group treated exclusively with NaF) a depression of CNS activity expressed as increased maze clearing time (table II; figure 5).

7CH homeopathic remedy, administered alone or in association with

0.25 mg NaF, has shortened maze clearing time (table II; figure 5), comparatively with the group treated exclusively with 0.25mg NaF, statistically significant ($p < 0.0001$) both for males and females.

Evaluation 3 - generation F2

For the second generation offspring, in which fluorine was provided exclusively from within the system (taken over from first generation), it can be noted that passed-over sodium fluoride induced a depression in CNS, expressed as increased maze clearing time, both in males and females. The most intense depressing effect was observed for males, in which maze clearing time is greater by 385.33% (previous generation dose 0.5 mg NaF) and even by 869.60% (previous generation dose 0.25 mf NaF), compared to control group (figure 6).

For male offspring from ascendants treated with 7CH homeopathic remedy, alone or in association with allopathic NaF, the depressing effect on CNS is greater compared with the one for the group of offspring from ascendants treated exclusively with 0.5 mg NaF (figure 7). Oppositely, a reduction in maze clearing time was registered for male treated with 7CH remedy which are the offspring of ascendants treated with 0.25 mg NaF (figure 7).

Conclusions

Experimental results highlighted the fact that, for females treated with different doses of NaF, the maze clearing time decreased, statistically significant, against control group, in all evaluations performed.

During evaluation 1 (young animals) it was underlined that administering 0.25 mg NaF has induced statistically significant ($p < 0.0001$) stimulation of CNS activity in male group 2F – 0.25 mg NaF), expressed by reduced maze clearing time against control group. For female group, the same NaF dose produced an increased in the said parameter, as an expression of CNS depressed activity.

Administration of 0.25 mg NaF has produced CNS effects, different with gender: stimulation in males and inhibition in females. The results from classic maze test correlate to morpho-pathological alterations observed in cerebral structures: discrete necrosis of cortex neurons, neuron satellitosis, vacuolar degeneration in cortex, a.s.o.

Homeopathic 7CH remedy, administered in young offspring of females treated with NaF in 0.25 – 0.5 mg doses, produced a CNS depression, expressed as increased maze clearing time against control group, both in males and in females.

Association between homeopathic 7CH remedy and 0.25 mg NaF has produced, exclusively in females, a statistically significant reduction of maze clearing time against control group, as an expression of CNS activity stimulation.

During evaluation 2, at which the animals of first generation (F1) reached developmental performances of adult age, the treatment with 0.25 mg NaF had the same CNS depressing effect for both group genders (males and females), as happened as young animals during evaluation 1.

Different effect were registered for 0.5 mg NaF, on one hand depressing CNS activity in females and on the other hand stimulating CNS activity in males (shortened maze clearing time).

Homeopathic 7CH remedy, administered alone or in association with 0.5 mg NaF, has induced (against group treated exclusively with NaF) a depression of CNS activity, expressed as increase in maze clearing time, both in males and also in females.

Homeopathic 7CH remedy, administered alone or in association with 0.25 mg NaF, has induced (against group treated exclusively with NaF) a depression of CNS activity, expressed as increase in maze clearing time, both in males and also in females.

For offspring resulted from second generation (F2), in which fluorine is exclusively passed over from ascendants (generation 1), it was observed that passed over fluorine induced a depression of CNS activity expressed as increased maze clearing time, both in males and also in females.

Treatment of ascendants with homeopathic 7CH remedy induced different effects on CNS performances for the second generation (F2), as follows:

- depression in males resulting from females treated with 0.5 mg NaF;
- stimulation in males resulting from females treated with 0.25 mg NaF.

It is worth observing that sodium fluoride administration in young animals resulted from ascendants treated with the same substance modifies CNS performances regarding investigative capacity depending on dose, gender and age.

For homeopathic 7CH remedy, the effects on first generation (F1) are different depending on physical development of animals and on NaF doses administered to ascendants, as follows:

- administered in young animals (evaluation 1), it depresses CNS activity expressed as increased maze clearing time, both in males and in females;

- administered in adult animals, alone or in association with 0.25 mg NaF, it stimulates CNS activity, both in males and in females.

In the case of the untreated animal generation (second generation - F2), in which fluorine is exclusively passed over from previous generations, sodium fluoride induces depression of CNS activity. To this generation homeopathic 7CH remedy has induced in males either depression or stimulation, depending on the administered NaF dose (0.25 – 0.5 mg).

In conclusion, sodium fluoride administration in allopathic, homeopathic or combined type allopathic/homeopathic, induces modification in investigative behavior, in a sense and to an extent dependant on dose, gender, physiological state and physical developmental stage. The behavioral modifications are in correlation with anatomo-pathological alterations documented at different levels in cerebral structures.

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Manuscript received: October 8th 2012