IJPSR (2024), Volume 15, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 June 2023; received in revised form, 15 July 2023; accepted, 21 November 2023; published 01 January 2024

CHRONIC EFFECTS OF ORAL SODIUM FLUORIDE ON MODELS OF COGNITION IN ADULT MICE

A. R. Harikrishnan [1], R. Arathy [*2] and Sunitha Messaline [2]

Drug Safety Physician [1], Apcer Life Sciences, Mondeal Heights, 1601 & 1602, Wing A, Iskcon cross Rd, Ramdev Nagar, Ahmedabad - 380015, Gujarat, India.
Department of Pharmacology [2], Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum - 695607, Kerala, India.

Keywords:

Mice, Animals, Sodium fluoride, Flouridation, Cognition

Correspondence to Author:
Dr. R. Arathy

Associate Professor,
Department of Pharmacology,
Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum - 695607, Kerala, India.

E-mail: arathy.r@gmail.com

ABSTRACT: Background: Sodium fluoride (NaF) is an inorganic fluoride salt used for the treatment of dental caries topically. It is also used in water fluoridation to prevent tooth decay. It has been reported to be associated with a lot of harmful effects, including neurotoxic effects. The aim of our study was to evaluate the chronic effects of NaF on the models of cognition in adult mice. **Methods:** Forty mice were randomly divided into four equal groups. NaF was administered dissolved in drinking water. The control group was Group I and received distilled water. Oral NaF at doses of 10mg/L, 20mg/L and 30mg/L respectively was given to Group II, Group III, Group IV. The influence of fluoride exposure on cognition was assessed using forced alternation test and spontaneous alternation test using Y-Maze. Evaluation was done at baseline, at the end of one month, two months and three months of NaF administration. Statistical analysis was done with the help of the Wilcoxon Signed Rank Test (within the group), Kruskal Wallis Test (between-group) and Mann-Whitney U Test. For all statistical analysis, p value<0.05 was taken as the threshold for statistical significance. **Results:** Animals receiving NaF at a dose of 10mg/L, 20mg/L and 30mg/L showed a significant decrease in the percentage of alternations in forced alternation test as compared to the control group with a p<0.01. Animals receiving NaF at a dose of 10mg/L, 20mg/L and 30mg/L showed a significant decrease in the percentage of alternations in spontaneous alternation test as compared to the control group with a p<0.01. **Conclusion**: Chronic use of oral NaF in adult mice may lead to cognitive impairment.

INTRODUCTION: Fluoride is the 13th most plentiful element present in the earth's crust [1]. It is a halogen. It is naturally present in water, soil, animals and plants [2]. Trace amounts are found in teeth and bone. Flouride has role in several enzymatic reactions[2]. Water is an essential medium that delivers fluoride. Fluoride toxicity occurs during water fluoridation, either naturally or added.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(1).105-11

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(1).105-11

In drinking water, the suggested optimal fluoride level is 0.7 mg/l [3]. Based on geographical regions, fluoride concentration in water varies. "The BIS standard for fluoride content is 1-1.5 mg /l" [4]. Sodium fluoride is an inorganic fluoride salt used for the treatment of dental caries or in municipal water fluoridization systems [5].

In the hydroxyapatite of tooth enamel, fluoride tends to bind to calcium ions, preventing acid corrosion of the tooth enamel. Despite its beneficial effects, prolonged exposure to higher concentration of fluoride can cause dental fluorosis, skeletal fluorosis, arthritis, muscle damage, osteoporosis, fatigue and can damage heart, arteries, kidney, liver, endocrine system and nervous system [6, 7, 8].

Carcinogenic potential of fluoride is not established [9].

Relevance of the Study: The role of environmental toxicity in the etiopathogenesis of cognitive disorders is not very well studied. Low level of exposures to toxins can cause cumulative effects over time. This can cause degeneration of brain and nervous system resulting in ill health. Apoptotic events [10] can occur in brain and nervous system after exposure of long duration. Hence this study was undertaken to evaluate the effects of 3-month oral administration of NaF in experimental models of cognition.

Aims and objectives:

Aims: To evaluate the effects of oral administration of NaF in experimental models of cognition for three months.

Primary Objective: To evaluate the effects of oral administration of NaF at doses of 10, 20 and 30 mg/L daily for 3 months in experimental models of cognition in adult mice Calculation of Sample size. done using G* POWER ® version 3.1.9.2, using repeated measures ANOVA as the test of significance assuming an α of 0.05, power of 95%. Assuming a 10% attrition rate, the corrected sample size was calculated using the formula [sample size /1- (attrition/100) 10 [11]. 10 animals in each group were the minimum number of animals required to detect statistically significant difference between groups and within the group in behavioral models.

10 animals were required in the negative control group to detect changes between the groups to avoid bias due to individual variation. So total number of 40 animals were required.

MATERIAL AND METHODS: The study was reviewed and approved by the institutional animal ethics committee, Sree Gokulam Medical College, Venjaramoodu, Trivandrum and the reference number of approval was SGMC-IAEC No.003/08aM/M2/2018

Experimental Design: The study was done as a prospective interventional study to explore the chronic effects of NaF. It was done in the animal house of Sree Gokulam Medical College, Venjaramoodu, Trivandrum. After the mice were quarantined and acclimatized for the initial 2 weeks period, they were randomly allocated into 4 groups. All the animals were kept in standard cages in groups of 10 and received access to chow diet and RO water *ad-libitum*. NaF was administered dissolved in drinking water at different doses.

The Groups Studied were:

Group A (n=10): Animals were receiving RO water and standard laboratory diet *ad libitum* and served as negative controls.

Group B (n=10): NaF was dissolved in RO water at 10 mg/L dose.

Group C (n=10): NaF was dissolved in RO water at 20 mg/L dose.

Group D (n=10): NaF was dissolved in RO water at 30 mg/L dose [11].

Assessment of cognitive function was done at baseline, one month, two months and three months of NaF administration. Animals in this experimental study consisted of 40 three-month-old male swiss albino mice of weight 20 to 30 g. They were obtained from Sree Chitra Thirunal Institute of Medical Sciences & Technology, Biomedical Technology Wing, Satelmond Palace, Poojappura, Trivandrum, Kerala - 695 012. Reg No: 98/GO/R-SL/BiS/99/CPCSEA. The experiment was done after a stabilisation period in the animal house at Sree Gokulam Medical College, Venjaramoodu, Trivandrum for fourteen days. Polycarbonate cages were used to keep the mice. In the room, humidity level was maintained between (50 ± 5%) and temperature between (22 ± 2 °C). The mouse had a 12-hour light and dark cycle. The mouse received laboratory pellet chow and water *ad libitum* and divided into four groups consisting of 10 mice per group.

The influence of fluoride exposure on cognition was assessed using forced alternation test and spontaneous alternation test.

Forced Alternation Test using Y-maze: A symmetrical Y-maze was used to perform this test. The dimensions of each arm of Y-maze were as follows; length 35cm, width 5cm and height 10 cm. The wall at the end of each arm had a distinct black and white pattern. The testing area was dimly lit to decrease apprehension in the mice.

The animals were handled for three days prior to testing. A sample trial (T1) was done for 5-minutes followed by retrieval trial (T2) for 5 minutes. In T1, the mouse was placed into the end of the start arm, in front of the wall, away from the centre.

The mouse was allowed to explore both arms of the Y-maze, while the third arm was blocked. After the sample run, the mouse was returned to its cage for 30-minutes before the next trial. In T2, the third arm was unblocked, the mouse was placed into the start arm, and then allowed to access all 3 arms of the maze. If a mouse ascended on the maze wall, it was immediately placed back into the abandoned arm.

After each trial, the maze was cleaned with 75% alcohol with a 75% alcohol to avoid odour indications. One arm entry was recorded only when 85% of a mouse's body entered the arm. Time in Novel Arm [%] was defined as the total time spent in the novel arm divided by the time spent in all arms during the first minute of the retrieval trial. Forced alternation [%] was calculated as the percentage of mice entering first the new arm during retrieval trial [12, 13].

Spontaneous Alternation Test (Y-Maze): The Y-maze apparatus was turned by 45° in this test. The test was done as a single 5-minute trial. The mouse was permitted to freely explore all the arms of the Y-maze.

If a mouse ascended on the maze walls, it was placed back into the arm. Each animal was placed into a different arm at the beginning of the trial. This was done to prevent any placement bias. Spontaneous Alternation [%] was calculated as successive entries in 3 different arms (ABC), divided by total number of possible alternations. The number of possible alternations is estimated by total count of entries minus two [12, 14, 15].

At the end of the experiment, the mice were euthanised by CO_2 inhalation. All experiments were done in agreement with the CCSEA (Committee for Control and Supervision of Experiments on Animals) guidelines for the use of small animals in biomedical research.

Statistical Analysis: Categorical variables were expressed as frequency and quantitative variables were expressed as mean ± SD. Wilcoxon signed Rank test [16] was used to assess the within-group effect of different doses of oral sodium fluoride on cognitive function in adult mice.

Kruskal-Wallis Test [17] and Mann-Whitney U Test [18] were used to compare the between-group effect of different doses of oral sodium fluoride on cognitive function in adult mice. For all statistical analysis, p value<0.05 was considered as statistically significant. Statistical software package SPSS, version 20.0 was used to complete the statistical analyses.

RESULTS:

Forced Alternation Test using Y-Maze: The effects of three-month oral administration of NaF at doses of 10mg/L,20mg/L and 30mg/L on % alternations in forced alternation test compared to control is shown in **Table 1.**

TABLE 1 EFFECTS OF 3-MONTH ORAL ADMINISTRATION OF NAF AT DOSES OF 10MG/L, 20 MG/L AND 30 MG/L ON % ALTERNATIONS IN FORCED ALTERNATION TEST COMPARED TO CONTROL

	Control		10mg/L		20mg/L		30mg/L	
Forced alternation test	Mean ± SD (% alternations)	Z$	Mean ±SD (% alternations)	Z$	Mean ± SD (% alternations)	Z$	Mean ± SD (% alternations)	Z$
Baseline	39.6 ± 4.2	-	39.6 ± 4.3	-	41.2 ± 3.5	2.21*	39.3 ± 3.7	-
1 month	35.5 ± 3.8	1.97*	34.1 ± 4.7	2.41*	35.3 ± 2.2	2.23*	33.1 ± 3.9	2.54*
2 month	36.6 ± 7.6	1.06	28 ± 4.5	2.37*	27.7 ± 3.3	2.2*	26.6 ± 1.7	2.52*
3 month	36.1 ± 4.9	1.54	23 ± 3	2.37*	21.8 ± 3.8	-	20.1 ± 1.7	2.53*

$ wilcoxon signed rank test *: - significant at 0.05 level Group A (control) did not show any significant difference in percentage of alternations while group B (10mg/L NaF), group C (20mg/L NaF) and group D (30mg/L NaF) showed marked decrease in percentage of alternations compared to their baseline values, maximum with group D.

The comparison of % alternations in forced alternation test after oral administration of NaF at doses of 10, 20 and 30 mg/L daily for 3 months in experimental models is shown in **Table 2.**

TABLE 2: COMPARISON OF % ALTERNATIONS IN FORCED ALTERNATION TEST AFTER ORAL ADMINISTRATION OF NAF AT DOSES OF 10, 20 AND 30 MG/L DAILY FOR 3 MONTHS IN EXPERIMENTAL MODELS

Group	Mean ± SD(% alternations)	Median (IQR)	$x^2$$	Mann-Whitney U Test P			
					Pair	Z#	p
Control (A)	-3.5 ± 5.5	-3.5 (-5.75 - -2)	18.14	p<0.01	A &B	3.13**	0.002
NaF 10 mg/L(B)					A & C		
	-16.6 ± 3.3	-16 (-17 - -15)				3.1**	0.002
NaF 20 mg/L(C)					A & D		
	-19.3 ± 3.8	-19 (-22.75 - -15.75)				3.37**	p<0.01
NaF 30 mg/L(D)					B & C		
	-19.1 ± 2.9	-18.5 (-22.5 - -16.25)				1.22	0.221
					B & D	1.65	0.100
					C & D	0.06	0.948

$ Kruskal Wallis Test, # Mann-Whitney U Test **: - Significant at 0.01 level.

The difference in the percentage of alternations between each study group was analysed using the Mann-Whitney U test. Animals receiving NaF at a dose of 10mg/L, 20mg/L and 30mg/L showed a significant decrease in the percentage of alternations as compared to the control group with a p<0.01. But there is no significant change in the percentage of alternations between Group B, Group C, and Group D. **Fig. 1** shows the comparison of % alternations in Forced alternation test after oral administration of NaF at doses of 10, 20 and 30 mg/L daily for 3 months in experimental models of cognition.

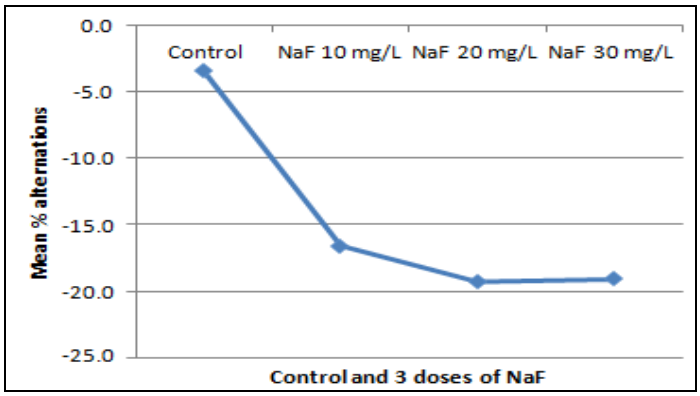

FIG. 1: COMPARISON OF % ALTERNATIONS IN FORCED ALTERNATION TEST AFTER ORAL ADMINISTRATION OF NAF AT DOSES OF 10, 20 AND 30 MG/L DAILY FOR 3 MONTHS

Spontaneous Alternation Test using Y-Maze: Table 3 shows the effects of 3-month oral administration of NaF at doses of 10mg/L,20 mg/L and 30mg/L on % alternations in spontaneous alternation test compared to control. **Table 4** shows the comparison of % alternations in spontaneous alternation test after 3- month oral administration of NaF at doses of 10, 20 and 30 mg/L daily in experimental models.

TABLE 3: EFFECTS OF 3-MONTH ORAL ADMINISTRATION OF NAF AT DOSES OF 10MG/L,20 MG/L AND 30MG/L ON % ALTERNATIONS IN SPONTANEOUS ALTERNATION TEST COMPARED TO CONTROL

	Control		10mg/L		20mg/L		30mg/L	
Spontaneou salternation	Mean ± SD (% alternations)	Z$	Mean ±SD (% alternations)	Z$	Mean ± SD (% alternations)	Z$	Mean ± SD (% alternations)	Z$
Baseline	61.8 ± 7.6	-	71.7 ± 4.6	-	69.5 ± 4.8	-	67.8 ± 7	-
1 month	66.1 ± 5.8	1.34	60.6 ± 3.8	2.37*	59.5 ± 5.6	2.2*	55.9 ± 7.8	2.53*
2 months	64.1 ± 9.3	0.77	52.7 ± 5	2.37*	50.2 ± 2.5	2.2*	47 ± 4.2	2.52*
3 months	56.6 ± 9.1	1.4	44.1 ± 4.3	2.38*	41.5 ± 2.7	2.21*	36.6 ± 5.2	2.52*

Group A(control) did not show any significant difference while group B (10mg/L NaF), group C (20mg/L NaF) and group D (30mg/L NaF) showed marked decrease in percentage of alternations to their baseline values. The decrease in percentage of alternations was maximum in group D.

TABLE 4: COMPARISON OF % ALTERNATIONS IN SPONTANEOUS ALTERNATION TEST AFTER 3- MONTH ORAL ADMINISTRATION OF NAF AT DOSES OF 10, 20 AND 30 MG/L DAILY IN EXPERIMENTAL MODELS

Group	Mean ± SD(% alternations)	Median (IQR)	$X^2$$	p	Mann-Whitney U Test Pair	Z#	p
Control (A)	-5.1 ± 9.6	-6.5 (-14.75 - 4.5)			A &B	3.25**	0.001
NaF 10 mg/L(B)					A & C		
	-27.6 ± 3.2	-26 (-31 - -26)				3.1**	0.002
NaF 20 mg/L(C)			17.33	p<0.01	A & D		
	-28 ± 5.5	-28 (-33.5 - -22)				3.36 **	p<0.01
NaF 30 mg/L(D)					B & C		
	-31.1 ± 7.8	-29.5 (-38.75 - -24.5)				0	1.000
					B & D	0.59	0.555
					C & D	0.78	0.433

$ Kruskal Wallis Test, # Mann-Whitney U Test **: - Significant at 0.01 level.

The difference in the percentage of alternations between each study group was analysed using the Mann-Whitney U test. Animals receiving NaF at a dose of 10mg/L, 20mg/L and 30mg/L showed a significant decrease in the percentage of alternations as compared to the control group with a p<0.01. But there is no significant change in the percentage of alternations between Group B, Group C, and Group D. **Fig. 2** Comparison of %alternations in Spontaneous alternation test after 3-month oral administration of NaF at doses of 10, 20 and 30 mg/L daily.

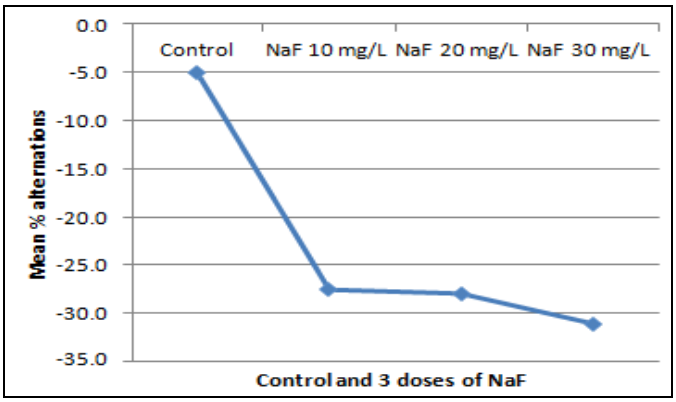

FIG. 2: COMPARISON OF %ALTERNATIONS IN SPONTANEOUS ALTERNATION TEST AFTER 3-MONTH ORAL ADMINISTRATION OF NaF AT DOSES OF 10, 20 AND 30 MG/L DAILY

DISCUSSION: In this study, varying concentrations of NaF were dissolved in the drinking water of adult mice and were investigated in models of cognition for 3 months. Major findings in this study were that sodium fluoride in adult mice may lead to cognitive abnormalities. Forced alternation and spontaneous alternation tests revealed that there may be cognitive abnormalities associated with chronic sodium fluoride intake in adult mice. In a study done by Liu *et al.* in young mice with lower doses of NaF found that mice developed retention memory deficits in Morris water maze experiment suggesting cognitive impairment [19]. Other studies that have explored the underlying mechanisms found that surplus amounts of fluoride can pass through the blood-brain barrier and cause a negative impact on the brain. McPherson *et al.* did a study on male rats treated with sodium fluoride at different doses. They did not find any cognitive abnormalities on forced alternation test [20].

Cao *et al.* did another study on learning and memory in fluoride-treated mice using Morris water maze and they found that fluoride exposure, even at a lower concentration, can aggravate the deficit in learning and memory [21]. Bittencourt *et al* [22] studied the effect of prolonged exposure of low level of fluoride (10 mg/L) and high level of fluoride (50 mg/L) in cognition in mice. They found that low level exposure did not produce cognitive impairment whereas high level exposure produced memory and learning deficits. Bartos *et al* [23] studied the effect of perinatal exposure of fluoride in rat and found that there was memory impairment in offspring rats. Yuan et al studied the effect of fluoride exposure using Y maze and found there was impairment in learning ability in mice [24].

The various mechanisms of fluoride induced brain injury are oxidative stress, neuronal apoptosis, imbalance of neurotransmitters and accumulation of pathogenic proteins [25]. The metaanalysis done by Miranda *et al* found that evidence available as of now is inadequate to propose an association between fluoride exposure and neurological disorder in humans [26].

CONCLUSION: Chronic oral NaF in adult mice may lead to cognitive abnormalities. Therefore, attention has to be paid to the adverse neurological effects of fluoride used to fight dental caries, and interest ought to be paid to the use and dosage of fluoride. Our findings endorse that unrestricted fluoride consumption is to be prevented to control its unfavourable effects. Further long-term studies may be necessary to confirm these effects.

ACKNOWLEDGEMENTS: The authors are thankful to Sree Gokulam Medical College & Research Foundation, Venjaramoodu for providing necessary facilities in the animal house for performing the research.

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Fluorine - an overview Science Direct Topics. https://www.sciencedirect.com/topics/earth-and-planetary-sciences/fluorine (accessed Dec. 02, 2020).
2. Kanduti D, Sterbenk P and Artnik B: Fluoride: a review of use and effects on health. Mater. Socio- Medica 2016; 28(2). doi: 10.5455/msm.2016.28.133-137.
3. Ullah R, Zafar MS and Shahani N: Potential fluoride toxicity from oral medicaments: A review. Iran J Basic Med Sci 2017; 20(8): 841–848. doi: 10.22038/IJBMS.2017.9104.
4. Peckham S and Awofeso N: Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention. Scientific World Journal 2014; 293019. doi: 10.1155/2014/293019. PMID: 24719570; PMCID: PMC3956646.
5. National Research Council. 2006. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. Washington, DC: The National Academies Press. https://doi.org/10.17226/11571
6. Solanki Y S, Agarwal M, Gupta A B, Gupta S and Shukla P: Fluoride occurrences, health problems, detection, and remediation methods for drinking water: A comprehensive review. Science of The Total Environment 2022; 807(1): 150601.https://doi.org/10.1016/j.scitotenv.2021.150601
7. Cury JA, Ricomini-Filho AP, Berti FLP and Tabchoury CPM: Systemic Effects (Risks) of Water Fluoridation. Braz Dent J 2019; 30(5): 421-428 http://dx.doi.org/10.1590/0103-6440201903124
8. World Health Organization. Inadequate or excess fluoride: a major public health concern. (WHO/CED/PHE/EPE/19.4.5)[2019-05-01] https://www.who.int/publications/i/item/WHO- CED-PHE-EPE-19.4.5
9. Anon American Cancer Society. Water Fluoridation and Cancer Risk. (cancer.org| 1.800.227.2345) [2022-08–17] https://www.cancer.org/healthy/cancer-causes/ chemicals/water-fluoridation-and- cancer-risk.html
10. Ottappilakkil H, Babu S, Balasubramanian S, Manoharan S and Perumal E: Fluoride Induced Neurobehavioral Impairments in Experimental Animals: a Brief Review. Biol Trace Elem Res 2023; 201: 1214–1236. https://doi.org/10.1007/s12011-022-03242-2
11. Charan J and Kantharia ND: How to calculate sample size in animal studies? J. Pharmacol. Pharmacother 2013; 4(4). doi: 10.4103/0976-500X.119726.
12. Wolf A, Bauer B, Abner EL, Ashkenazy-Frolinger T and Hartz AMS: A Comprehensive Behavioral Test Battery to Assess Learning and Memory in 129S6/Tg2576 Mice. PloS One 2016; 11(1): 0147733. doi: 10.1371/journal.pone.0147733. PMID: 26808326; PMCID: PMC4726499.
13. Wolf A, Bauer B, Erin LA, Tal AF, Hartz MS and Anika: Forced Alternation (Y-Maze). PLOS ONE 2016. Figure. https://doi.org/10.1371/journal.pone.0147733.g002
14. Stanford Behavioral and Functional Neuroscience Laboratory. Y maze spontaneous alternation test. Available at: https://med.stanford.edu/sbfnl/services/bm/lm/y-maze.html (Accessed: 14 July 2020).
15. Kraeuter AK, Guest PC and Sarnyai Z: The Y-Maze for Assessment of Spatial Working and Reference Memory in Mice. Methods Mol Biol. 2019; 1916:105-111. doi: 10.1007/978-1-4939-8994-2_10. PMID: 30535688.
16. Wilcoxon Signed Ranks Test - an overview | ScienceDirect Topics. https://www.sciencedirect.com/topics/medicine-and-dentistry/wilcoxon-signed-ranks-test (Accessed: Dec. 01, 2020).
17. Kruskal-Wallis H Test in SPSS Statistics | Procedure, output and interpretation of the output using a relevant example. https://statistics.laerd.com/spss-tutorials/kruskal-wallis-h-test-using-spss- statistics.php (Accessed: Dec. 01, 2020).
18. Mann-Whitney U Test - an overview | ScienceDirect Topics. https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/mann-whitney-u- test (Accessed: Dec. 01, 2020).
19. Liu F, Ma J, Zhang H, Liu P, Liu YP, Xing B and Dang YH: Fluoride exposure during development affects both cognition and emotion in mice. Physiol Behav 2014; 124: 1-7. doi: 10.1016/j.physbeh.2013.10.027. Epub 2013 Oct 30. PMID: 24184405.F.
20. McPherson CA, Zhang G, Gilliam R Brar SS, Wilson R, Brix A, Picut C and Harry GJ: An Evaluation of Neurotoxicity Following Fluoride Exposure from Gestational Through Adult Ages in Long-Evans Hooded Rats. Neurotox Res 2018; 34(4): 781-798. doi: 10.1007/s12640-018-9870-x. Epub 2018 Feb 5. PMID: 29404855; PMCID: PMC6077107.
21. Cao K, Xiang J, Dong YT, Xu Y, Li Y, Song H, Zeng XX, Ran LY, Hong W and Guan ZZ: Exposure to fluoride aggravates the impairment in learning and memory and neuropathological lesions in mice carrying the APP/PS1 double-transgenic mutation. Alzheimers Res Ther 2019; 11(1): 35. doi: 10.1186/s13195-019-0490-3. PMID: 31010414; PMCID: PMC6477877.
22. Bittencourt LO, Dionizio A, Ferreira MKM, Aragão WAB, Cartágenes S de C, Puty B, Maia C dSF, Zohoori FV, Buzalaf MAR and Lima RR: Prolonged exposure to high fluoride levels during adolescence to adulthood elicits molecular, morphological, and functional impairments in the hippocampus. Sci Rep 2023; 13(1): 11083. https://doi.org/10.1038/s41598-023-38096-8
23. Bartos M, Gumilar F, Gallegos CE, Bras C, Dominguez S, Cancela LM and Minetti A: Effects of Perinatal Fluoride Exposure on Short- and Long-Term Memory, Brain Antioxidant Status, and Glutamate Metabolism of Young Rat Pups. Int J Toxicol 2019; 38(5): 405-414. doi:

10.1177/1091581819857558. Epub 2019 Jun 20. PMID: 31220985.

24. Yuan J, Li Q, Niu R and Wang J: Fluoride exposure decreased learning ability and the expressions of the insulin receptor in male mouse hippocampus and olfactory bulb. Chemosphere 2019; 224: 71- 76. doi.org/10.1016/j.chemosphere.2019.02.113.
25. Ren C, Li HH, Zhang CY and Song XC: Effects of chronic fluorosis on the brain. Ecotoxicol Environ Saf 2022; 244: 114021. doi: 10.1016/j.ecoenv.2022.114021. Epub 2022 Aug 29. PMID: 36049331.
26. Miranda GHN, Alvarenga MOP, Ferreira MKM, Puty B, Bittencourt LO, Fagunades NCF, Pessan JP, Buzalaf MA R and Lima RR: A systematic review and meta-analysis of the association between fluoride exposure and neurological disorders. Sci Rep 2021; 11: 22659. https://doi.org/10.1038/s41598-021-99688-w

How to cite this article:
Harikrishnan AR, Arathy R and Messaline S: Chronic effects of oral sodium fluoride on models of cognition in adult mice. Int J Pharm Sci & Res 2024; 15(1): 105-11. doi: 10.13040/IJPSR.0975-8232.15(1).105-11.