Short-term impact of anthropogenic environment on neuroplasticity

Discussion & Summary

Chapter 5: Discussion and Summary

About 10.7% of the global population suffers from a mental disorder. Concerning anxiety disorders, globally, 301.39 million prevalent cases were estimated in 2019 (1). Neuroscience research reveals that different mental health disorders such as stress, anxiety, depression, and even neurodegeneration and their forthcoming behaviors are associated with alterations in neuroplasticity. Thus, it is important to collect evidence regarding the etiological factors and if possible, design prevention and treatment strategies for this altered neuroplasticity. The plasticity of the human brain is adaptive to structural and functional changes based on experience and training leading to functional recovery (2).

Among the various factors that affect neuroplasticity, human physiology and health are strongly influenced by the environment. Several factors modulate neuroplasticity in a positive and negative direction. The field of environmental health has evolved significantly in the recent past but is still based on epidemiological studies. Most studies have focused on the potential negative impacts of environmental factors (mainly social stress and exposure to chemicals), but some factors have positive effects. Thus, it was planned to study one positive and one such negative stimuli on neuroplasticity in this thesis. In the first chapter **(Chapter 1)**, the concepts of neuroplasticity, anthropogenic factors, and exposome are introduced. The process of neurogenesis during development and adulthood is then discussed, indicating the vulnerability of the developing brain to exposome. Then the exposure of human beings and animals to different anthropogenic stimuli is introduced. The factors that influence neuroplasticity are detailed. Specific emphasis is laid on the impact of acoustic and chemical stimuli on neuroplasticity. Our objective was to gain more knowledge about the physiological impact of potentially positive (auditory stimulation: music) and negative (chemical exposure: thiacloprid) stimuli on the peripheral and central nervous systems.

Among the different stimuli that have shown beneficial effects, music is a promising intervention that is ubiquitous across human cultures. Music is a powerful sensory stimulus that produces physiological, psychological, and social effects. Both listening to music and music playing lead to structural and functional neuroplastic changes that are utilized in the management of different non-communicable disorders.

Music listening involves the sensory processing of acoustic stimuli (peripheral nervous system) followed by cognitive and emotional processing in a neural network (central system) producing pleasurable physical and emotional experiences. However, the association between acoustic intervention with music, its effects on overall health, and the mechanisms behind it remain unclear, and earlier studies reported contrasting findings. Thus, we asked the question: **What are the short-term effects of positive anthropogenic auditory stimuli (music) on physiological parameters among healthy human beings? In Chapters 2 and 3,** the effects of auditory stimuli (music) were studied on the central and autonomic nervous system, through the analysis of subjective measures of stress and anxiety, and of physiological parameters (electrocardiography, blood pressure, and electroencephalography recordings) in humans.

Chapter 2 details the study where we used a triple-blind, randomized control trial design and showed that listening to music led to behavioral and cardiovascular modifications among healthy young adults. This chapter demonstrated the effect of different musical acoustical stimuli (three modes of music stimuli, named *Miyan ki Todi, Malkauns, Puriya* in Indian music), compared to natural sounds in the environment (stimulus given to the control group), on measures of stress, anxiety, blood pressure control, and autonomic nervous system tone (measured employing heart rate variability) among healthy human beings. Modes are a combination of notes in a given scale of music woven together to produce a melody. The melody is the linear succession of musical tones that vary in pitch. We showed that all modes of music reduced the levels of anxiety and stress to different degrees. The control group did not show a change in anxiety levels. However, using heart rate variability measures, we observed that during the intervention with two modes (*Miyan ki Todi, Puriya)*, there was an arousal response, while after the intervention an improvement in parasympathetic tone (relaxation response) was observed. The third mode of music (*Malkauns)* caused a sustained increase in parasympathetic tone, like that observed in the control group. It indicated that although musical acoustic stimuli reduced anxiety and stress measures, the timing of autonomic changes varies with the mode used as the stimulus.

Dysautonomia refers to a group of medical conditions caused by problems with the autonomic nervous system (ANS). Worldwide, it affects more than 70 million people. Dysautonomia can affect ANS functions such as control of blood pressure, heart rate, respiration, gastrointestinal functions, all visceral organ functions, and temperature control. Secondary dysautonomia can result from different diseases such as Cancers, Diabetes, PD, Rheumatoid arthritis, Amyloidosis, and many such disorders. Currently, there is no cure for this condition except for symptomatic management of blood pressure (for example for low hypotension, more water and salt intake is prescribed) or other autonomic symptoms. The literature review suggests the use of supportive therapy modalities, including music as an intervention for the prevention or treatment of autonomic dysfunction (3). Interventions based on music therapy, traditional Chinese medicine-related treatments, exercise, relaxation, and myofascial release techniques are found to be beneficial. Many randomized controlled trials have reported that music possesses anxiolytic and analgesic properties, and is associated with decreased heart rate, respiration rate, and blood pressure in palliative care settings or perioperative periods. Regarding the mechanism behind the effect of auditory stimulation and cardiac autonomic regulation, it was hypothesized that pleasurable songs induce dopamine release in the striatal system, which is involved in autonomic regulation, and this topic has been well-reviewed in (4).

This is the first study to focus on how Indian modes can alter physiological measures related to stress, arousal, and anxiety. Clinically, this study promoted the idea of the use of music, and particular modes, to facilitate relaxation, and provide an alternative treatment strategy. Future studies may find it beneficial to expand the present findings to other melodies, investigate during live music concert sessions, analyze temporal variations in heart rate variability during the intervention, and more closely investigate gender differences to understand if reproductive steroid hormones can play a role in the physiological measures assessed. It would also be interesting to investigate factors related to perception and emotion, such as personality and music preferences, in future work. Further analysis of the musical features and the components (e.g., temporal analysis of note/tonal variations, pitch, tempo, dynamics, and contrast) of the music used may enhance our understanding of the physiological effects.

Musical stimuli can induce a variety of emotions in individuals. The mode is one of the most important structural features that constitute the expressional characteristics of music. The mode is a structural feature embodied in the structural relationship among the tones that constitute the basic series of music. Two of the modes are natural diatonic scales, the Ionian (Natural Major Scale) and the Aeolian (Natural Minor Scale). The remaining commonly used modes are Phrygian, Dorian, Mixolydian, and Lydian. In Indian music, modes are named *ragas*, and there are about 72 parent modes called the *Janaka ragas* (containing the 7 notes, *Sa Ri Ga Ma Pa Dha Ni*, similar to *Do Re Mi Fa So La Ti* of western music), derived from 22 music tones. From these modes are the thousands of other modes derived by either eliminating, adding, skipping a few notes, or by different permutations and combinations of the tones. The structural difference between the major and the minor mode produces distinct sound effects. It is important to understand these modes as the literature survey repeatedly suggests that the major mode tends to induce positive emotions, while the minor mode tends to induce negative emotions. For more on this see (5–7) which was also shown to be true using Indian music ragas (8,9). In the current study, though physiological effects varied with the modes heard, emotional ratings or valence recordings were not included to conclusively comment on the emotional experience the participants might have had. Thus, future studies may include studying modes of music and the emotional experience of the participant simultaneously.

In recent years, a lot of research has focused on the physiological effects of music. Electroencephalography (EEG) is often used to verify the influence of music on human brain activity. Music is considered a powerful brain stimulus, as listening to it can activate several brain networks. Music of different kinds and genres may have different effects on the human brain. Furthermore, the brain activity of multiple subjects has been shown to synchronize during salient moments of natural stimuli, suggesting that the correlation of neural responses indexes a brain state operationally termed 'engagement'. This is classically studied as Inter-subject correlation (ISC) using fMRI and has recently been used to analyze EEG signals on intervention with narrative stimuli, with a temporal structure such as a story, movie, or music.

In **Chapter 3** we analyzed the brain wave changes and frequency distribution spectral analysis (measured by EEG) by listening to the same set of acoustical stimuli used in chapter 2. On analysis of frequency components across the whole scalp during the intervention, a global drop in alpha power in all the groups and a frontocentral increase in beta (after intervention) and gamma power (during intervention) were noticed with modes *Miyan ki Todi* and *Malkauns* respectively. This change in beta was postulated to be due to attention modulation, and higher alertness. In EEG, the alpha rhythm is said to be associated with global cognitive engagement while beta and theta rhythms point towards specific functions, for example, working memory, and there is de-synchronization in alpha and beta bands during mental imagery (10). The rise in gamma was probably indicating the binding of music features or may also be due to liking the music based on previous literature. Group-based cluster statistics revealed a rise in left frontal gamma power during intervention with mode *Malkauns.* Group-based cluster statistics revealed a drop in the right frontoparietal delta (which could be due to alertness or divergent thinking following the stopping of the intervention) and a rise in frontal beta1 with mode *Miyan ki Todi*. With the mode *Puriya,* after the intervention, a widespread drop in delta power and a rise in frontal beta1 were observed.

It was further demonstrated that there existed three most correlated components, the first component representing delta or theta power (band1), the second component alpha or beta1 power (band2), and the third beta2 or gamma power (band3), with both modes *Malkauns* and *Miyan ki Todi* showing similar patterns of decrease in the lower frequency band (band1) and increase in mid-band (band2) during the intervention, compared to baseline and mode *Puriya* being similar to the control group, with an increase in the lower frequency band (band1) and decrease in mid-band (band2) during the intervention, compared to baseline. Shared brain responses among the participants as captured by Inter-subject correlations (ISC) were also studied in this chapter. Reduction in globally distributed low-frequency activity and increase in posterior dominant alpha-beta1 activity may be characteristic of passive listening to relaxing Indian modes, which may persist even after 10 minutes of the listening period. Among the modes, *raga Malkauns* showed this effect most prominently, followed by *raga Miyan ki Todi* and least by *raga Puriya*. As the increase in posterior alpha and low beta power

is associated with Default Mode Network (DMN) activity and a decrease in delta power with positive emotional memory, the spectral pattern we observed may indicate the observation of positive autobiographical memory while listening to musical modes, and thus contribute to a relaxing experience.

In a recent study, preferred music (called favorite music) and researcher-selected music (called relaxing music) were used as stimuli to study their effects on the brain. A better soothing effect was achieved by using relaxing music in that study, and it was also observed that longer periods of listening to relaxing music can cause a more significant change (11), which was further confirmed (12). When music pieces were played with two instruments, top-down modulations consistently enhanced or better reconstructed the relevant instruments than irrelevant ones during the segregation task. This wasn't the case with the integration task as listeners probably employed heterogeneous strategies. These findings are similar to those seen with speech and polyphonic music perception (13). Familiarity with music is another confounding variable in music studies. Human listeners exhibit marked sensitivity to familiar music. Pupil responses showed a greater and faster dilation rate to familiar music, consistent with a faster activation of the autonomic salience network. EEG showed a later differentiation of the tunes, from 350 ms after onset. Interestingly the cluster pattern identified in the EEG was very similar to that found in the classic memory retrieval paradigms, suggesting that the recognition of brief, familiar music snippets, drew on similar processes (14). Music listening has also been used to differentiate responses in EEG between major depression disorder (MDD) and healthy individuals. During music perception, MDD patients exhibited altered functional connectivity in delta and beta bands. MDD patients did not exhibit a lateralized effect while healthy people showed a left hemisphere-dominant phenomenon. These responses facilitate a new direction toward a diagnosis of connectivity disorders in depressed patients using music perception paradigms (15). Music of different valences has been shown to alter the EEG activity in emotion-specific regions (16). Music therapy and emotion-guided music decisions may be used for improving clinical depression and anxiety (17). Music has also been used to understand and elicit emotions in mental health conditions such as bipolar disorder, autism, and Alzheimer's disease (18–20). Recently EEG power with a higher beta band and gamma band at the O2 and P4

electrodes was used as evidence to conclude that sad music may alleviate pain (21), which also has potential value for clinical use. In PD patients EEG power differences are partially reduced by listening to music. Music slightly improved the connectivity differences, particularly the frontotemporal inter-hemispheric communication which might underlie music's beneficial effects on PD pathophysiology and should be further investigated (22). Brain development and morphological changes with age also influence the way sounds are processed, with studies showing an age-related increase in inter-subject variability (23). Neuroplastic effects of music-based interventions and their usage for neurorehabilitation were recently reviewed in (24).

The importance of studying changes in EEG on listening to music is thus not a new subject. In our current study, we showed that every mode of music can have a different physiological effect as observed on HRV (Chapter 2) or EEG recordings (Chapter 3). Further studies may include phenomenological reports to support these findings and build a stronger scientific foundation for the use of music in medicine. As ISC-based brain activity is modulated by training, studies may try to explore the effect of musical training and genre familiarity aspects. Different musical stimuli that are known to be emotionally stimulating can be studied, as ISC is said to vary with time-based emotional stimuli such as stories or movies. Studies may also include the emotion ratings for a better understanding of the exact emotions that might have caused these physiological changes. To exactly know the neural substrates activated within and between participants passively listening to the different scales, it is better to use higher-density EEG or fMRI data.

In the present thesis, we tried to understand the neuroplastic effects of one negative anthropogenic stimulus (insecticide) - **Chapter 4.** Industrialization of the agricultural sector has increased the chemical burden on natural ecosystems. Pesticides are agricultural chemicals used in agriculture, public health programs, and urban green spaces to protect plants and humans from various diseases. The intensive use of pesticides (eg: organophosphates, carbamates, pyrethroids, neonicotinoids) and the persistence of the molecule in the environment have contributed to the increased exposure of non-target invertebrates and vertebrates, including humans. For experimental studies, animals are commonly used to understand the negative impact of

anthropogenic stimuli on neuroplasticity. Among the various pesticides, though a handful of neonicotinoids were banned by the European Union, they continue to be used in some countries and they continue to persist in the environment. For the current thesis, we chose to study one of the most toxic, persistent insecticides, thiacloprid (**Chapter 4)**, where we highlight the developmental neurotoxic potential of this insecticide. Though studies have looked into the potential of neonicotinoids from a developmental neurotoxic potential point of view, not many have studied the same in the way that the results of those can be applied to human health as per European Protection Agency guidelines for the study of insecticides. The drawbacks of previous works were the absence of studying both sexes, at different doses and the absence of statistical analysis. Different areas of the brain, in particular, the cholinergic areas of the brain, that are the prime targets for neonicotinoids, for their gene transcription had not been explored before. Thus we asked the question, **what are the potential short-term neuroplastic effects (as evidenced by gene expression) after perinatal exposure to different doses of thiacloprid, a toxic anthropogenic stimulant neonicotinoid in animals, zebrafish, and mice** (Chapter 4)?

In Chapter 4, we evaluated the effect of perinatal exposure to different doses of thiacloprid, a neonicotinoid insecticide, on neuronal markers from whole heads of zebrafish larvae and specific brain regions (amygdala, hippocampus, cerebellum, hypothalamus) in mouse models. Perinatal exposure to thiacloprid resulted in the dose and sex-dependent alteration in the neuronal and steroid markers in specific brain areas only in mice, but not in zebrafish. In mouse offspring, a significant main effect of dose with an increase in DCX, PCNA (amygdala), PCNA (cerebellum), synaptophysin (Hypothalamus), and a decrease in hypothalamic ERβ, nestin, synapsin IIA, BDNF, Aromatase, hippocampal DCX, PCNA, neurogenin, aromatase, nestin, and synaptic markers was observed. The sex-specific difference in BDNF transcription in the hypothalamus and PCNA in the hippocampus was observed. Dose-dependent change (from 0.06 to 0.6 mg/kg/day) with an increase in synaptophysin (hypothalamus), ERα, ERβ, aromatase, nestin, neurogenin (hippocampus), and reduction in aromatase (amygdala), was observed. This work shows that alteration of the cholinergic system by neonicotinoid pesticide impacted the neuroendocrine system and the consequences of

this alteration should be further investigated in the central (limbic) and peripheral nervous system and on the pathophysiology in vertebrates, including humans.

Our objective was to define the potential impact of the neonicotinoid thiacloprid on neuroplasticity and the neuroendocrine system in two vertebrates: the zebrafish and the mouse. In our study, we did not see any impact of thiacloprid on zebrafish, independent of the dose while specific brain regions in mice were impacted by early exposure to this pesticide. Though several genes are expressed during the developmental stages of zebrafish, none of the gene expressions changed using three different concentrations of thiacloprid. The probable reasons this could be the dosage used (which was low compared to previous studies), the duration of exposure, the temperature during exposure, species sensitivity difference for the chemical, receptor affinity, dynamic regulation of the cholinergic system, or presence of chorion. Analysis of the effect of thiacloprid and other such neonicotinoids on cholinergic system transcripts and subunits of the receptors is proposed to be taken up in future studies. Oxidative stress was proposed to be one of the chief mechanisms for developmental neurotoxicity with neonicotinoids. Further studies in this regard will be valuable. Also, the dose for zebrafish needs to be titrated further to see the neurotoxic effects, if any. Long-term effects at the molecular level in the brain and behavior remain to be explored.

In mice, thiacloprid caused opposite effects on the hippocampus and the amygdala, regions chiefly involved in emotional behavior, memory, learning, fear, and stress responses. Further studies may try to elucidate the long-term behavioral modifications on developmental exposure to thiacloprid. Inflammatory response mounted by these regions may also be further elucidated in future studies. By thiacloprid effects on Estrogen receptors and aromatase, we postulated that thiacloprid may act through these ER receptors in a region and dose-specific manner to impair the functions in the hypothalamus while facilitating the functions of the hippocampus at the mid-dose range. At a high dose of thiacloprid, probable neuronal/glial cytotoxicity leads to a drop in most of the gene expressions. Recently, neonicotinoids, clothianidin, acetamiprid, and dinotefuran were shown to activate G-protein coupled Estrogen receptors (GPER) in a dose-dependent manner and thus promote breast cancer proliferation (25). It would be interesting to see if GPER in different brain regions is affected by neonicotinoids in future

studies. It is important to study the role of thiacloprid and other neonicotinoids on sex-dependent behaviors and their involvement in the epigenetic causation of neurological diseases, such as Alzheimer's disease in long term through their action as endocrine disruptors. In the current study, we found a rise in synaptophysin expression in the hypothalamus, indicating a probable rise in synaptic activity at that dose, but due to lack of further details, it is difficult to comment about a particular nucleus within the hypothalamus that might have been affected, or the neural activity change or the eventual protein expression. Despite high concentrations of these synaptic markers in different regions of the brain, we did not observe similar alterations in the expression in the various regions on exposure to thiacloprid. Future studies should include immunostaining procedures during developmental and later stages in mice models to ascertain these structural changes, if any, seen at neuronal and synaptic levels after gestational exposure to different doses of neonicotinoids. Combining behavioral analysis will help in confirming the neurological phenotypic pathologies associated with developmental neurotoxicity caused by thiacloprid and other neonicotinoids. Sex differences in exposure to neonicotinoids have often been ignored. Since several neurological diseases appear to occur in a sex-specific manner, studies on neonicotinoids must include sex as a biological variable. Furthermore, neonicotinoids could freely pass through the BBB and were detectable in the brain of mice (26,27). The results also indicate that thiacloprid may not be toxic to all cell types but affects each brain region differently and in a dose-dependent, sex-dependent manner. This may also be due to the specific subunit of nAchR present in these regions, their distribution, and the connection with other neurotransmitter systems. Differences between neuronal and glial responses to thiacloprid are yet to be elucidated.

This study is important as neonicotinoids are still the most commonly used insecticides that get incorporated into the physiology of the plants and thus cannot be cleaned off just by washing or cooking before consumption like surface insecticides. Furthermore, it should be noted that washing and peeling cannot completely remove residues. In the majority of cases, the concentrations do not exceed the legislatively determined safe levels. However, these 'safe limits' can underestimate the real health risk, as in the case of simultaneous exposure to two or more chemical substances, which

occurs in real-life conditions and can have synergistic effects. Pesticide residues have also been detected in human breast milk samples, and there are concerns about prenatal exposure and health effects in children. Insecticide safety should be determined and risks publicized before registration and introduction to the market. Testing for developmental neurotoxicity and general toxicity must be routine for all chemicals determined for human use. In general, the world must be encouraged to restrict or prohibit the use of synthetic products in the production of food (28). Alternatives to insecticide use must also be explored, such as the Cry protein (δ-endotoxin) produced by the *Bacillus thuringiensis*, Biosolarization, Plant-derived substances, Insect hormones, Certain food-grade oils, and other organic pesticides. We need to try to understand the impact of chemicals on non-target species and help to regulate the use of these molecules and find alternatives if (neuro)toxicity is present.

Future perspectives

Exposome research can facilitate the identification of particular environmental factors that contribute to the onset of neurological disorders. The impact of chemical exposures currently surpasses biological exposures, and until recently scientists mainly focused on the acute consequences of biological exposures. However, a crucial constraint of various exposome and health investigations so far is that they concentrate on the connections between individual components of the external exposome and unfavorable health outcomes. The mechanistic comprehension of the relationship between exposure and disease is disregarded in both epidemiological and toxicological studies. The recent exposome framework has propelled the domain of molecular toxicology by offering the necessary mechanistic examination of the exposome's effects on health (29). Understanding the mechanisms involved in developmental neurotoxicity should be used to develop focused therapeutic interventions. Furthermore, guidelines for testing developmental neurotoxicity may require re-evaluation. There is also a necessity to create and verify innovative sets of alternative models and tests for developmental neurotoxicity (see a recent review on risk assessment, alternate models, and recommendations (30)).

Neurotoxic effects are often observed as a result of exposure to toxic substances during pregnancy, nursing, early childhood, and adolescence. Although these effects

may manifest after only a brief period of exposure, research suggests that it may take months or even years for the detrimental effects of toxic substances to become clinically detectable. Therefore, similar to polio, tuberculosis, or any infectious disease detection or vaccination campaigns, it is crucial to conduct thorough epidemiological studies to establish risk assessments and possible causal associations between chemical exposures and developmental abnormalities in humans. To achieve this, it is necessary to quantitatively determine the relationship between internal exposure and exposome. Physiologically based pharmacokinetic (PBPK) and quantitative in vitro to in vivo extrapolation models can be used for this purpose (30). This will also aid in the early detection and treatment of neurological disorders, as well as the prevention of exposure risks. This involves analyzing how neurotoxicants interact with an individual's genetic susceptibility and exposure to other environmental factors. By understanding the interplay between various environmental factors and their impact on neurological health, exposome research can contribute to developing personalized prevention and precision medicine approaches that consider an individual's unique environmental exposures when treating neurological disorders. However, identifying silent neurotoxicity and subclinical changes remains a challenge, necessitating further research to develop tools for the early identification of exposure risks. It is essential to note that treating developmental neurotoxicity is often a multifaceted process that requires a team of healthcare professionals from various disciplines, including neurology, pediatrics, rehabilitation, and psychology. Exposome research can offer valuable insights to policymakers, enabling them to develop more effective public health policies that address environmental factors contributing to neurological disorders.

Although music therapy is effective in treating various neurological conditions such as stroke, traumatic brain injury, and Parkinson's disease, its efficacy in treating developmental neurotoxicity is uncertain. Developmental neurotoxicity can affect different aspects of neurological function, including cognitive, motor, and sensory processing abilities. Music intervention may help address certain areas such as improving motor coordination, communication, and socialization skills. However, the effectiveness of music therapy for developmental neurotoxicity would depend on the specific symptoms and underlying condition of the individual. Music can be used as an

adjunctive therapy alongside other treatments for the rehabilitation of individuals exposed to neurotoxins, providing a more comprehensive approach to treatment. Moreover, music has the potential to promote neurogenesis and neuroplasticity and thus may be beneficial for treating certain aspects of developmental neurotoxicity. Nevertheless, further research is necessary to establish the effectiveness and optimal use of music therapy in this context. Recent epigenetic studies have shown that music listening may upregulate microRNAs related to neuroplasticity, indicating a potential positive impact of music therapy as a way to counteract the negative impact of anthropogenic stimuli with positive ones (31). Future studies should look into the neuroplastic effects of music as an adjuvant in the management of people exposed to chemicals, including psychoactive substances.

Summary

- **In human studies,** we observed that musical acoustic stimuli have specific effects on the autonomic nervous system, stress, and anxiety levels. Specific modes *Miyan Ki Todi* and *Puriya* caused arousal during the intervention, while improving the parasympathetic tone after the intervention, while mode *Malkauns* led to a sustained rise in parasympathetic tone, as observed in the control group receiving natural sounds as stimuli.
- Neurophysiological study of electroencephalogram during the different modes of musical acoustic stimuli showed a higher level of engagement and attention during modes *Miyan Ki Todi* and *Puriya,* while mode *Malkauns* led to divergent thinking after the intervention. These studies confirmed the acute neuroplastic effects of auditory stimuli in human beings.
- **In animal studies,** we have observed that chemical environments, such as exposure to pesticides, can be causally linked to the alteration of the central nervous system. As shown in the present work and adding to the current literature, the impact of pesticides will depend on the animal model, the brain regions, and the sex of the model, reflecting the complexity of studying the consequences of chemical exposure on the nervous system and behavior and its extrapolation to the human when required.

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