Toxicology and Safety Pharmacology Investigations on the Nervous System: 2024 Industry Survey

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Abstract

Although there has been an increase in the FDA approvals of CNS therapeutics over the last few years, there is still a need to understand industry practices as they relate to neurotoxicity and safety testing of therapeutics given the potential severity of the mentioned risk and divergent approaches to evaluate product-induced risks. The American College of Toxicology (ACT), the Safety Pharmacology Society (SPS) and the Society for Toxicological Pathology (STP) conducted a survey in 2024 to assess industry practices for safety testing in the nervous system. The objective of this survey was to collect responses from participants across multiple regions across the world to understand the current landscape for safety testing in the nervous system. Respondents for the survey were based in Asia, Europe, and North America. The survey contained questions focused on the following areas: general CNS, drug abuse liability, peripheral nerve safety, and seizure liability. These questions were intended to understand practices related to the selection of in vitro and in vivo assays, animal species, as well as types of endpoints employed in nonclinical safety studies. The survey findings indicated that a wide variety of in vitro and in vivo assays were employed to evaluate drug-induced risks (e.g., seizures, ototoxicity, abuse liability, and peripheral nerve damage) in the nervous system; and that a variety of endpoints and other design features were employed in these and other studies based on factors that included the species tested, potential pharmacological/toxicological profile of the product tested, and the clinical dose schedule supported by data from pivotal nonclinical safety studies. Findings from the survey also indicated that drug-induced risks in the nervous system were due to alterations in various factors that include species anatomy and physiology, drug on/off target effects, and experimental procedures. Together, these findings illustrate that industry practices vary based on the numerous factors, which helps to explain the divergent approaches taken by companies to evaluate drug-related risks and the challenges related to translating animal findings across products (includes those from the same class).

Purpose of the 2024 Survey*

- Identify current industry practices as they relate to central, peripheral, and autonomic nervous system drug safety testing
- Compare results from 2024 survey to a similar survey conducted in 2015 (where applicable; Authier et al., J Pharmacol Methods 2016)
- Capture novel insights and trends related to findings shared

Differences between 2024 and 2015 surveys:

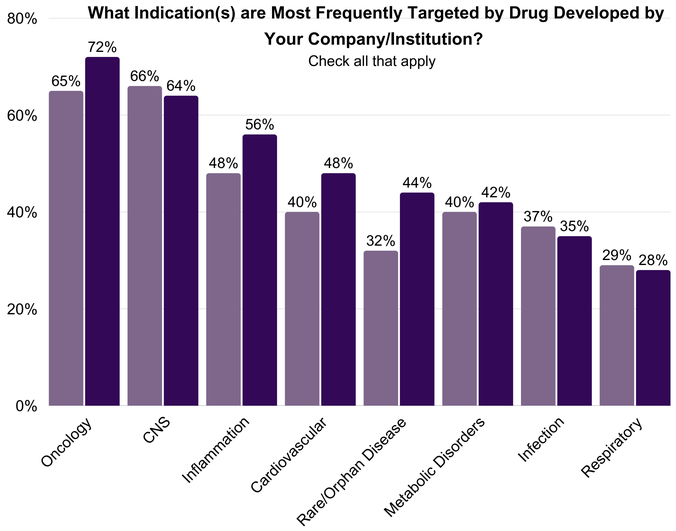
- Fewer questions provided in the 2024 vs. 2015 survey
- Questions in 2024 survey were more concise and focused vs 2015 survey
- 2024 survey was conducted via several organizations, unlike 2015 survey
- Fewer respondents for the 2024 vs. 2015 survey

Key Demographics for Survey Respondents

	2024	2015
Total Participants	n=130	n=158
Total Questions	n=30	n=55
Participants from Asia (%)	5%	16%
Participants from Europe (%)	32%	20%
Participants from North America (%)	64%	56%

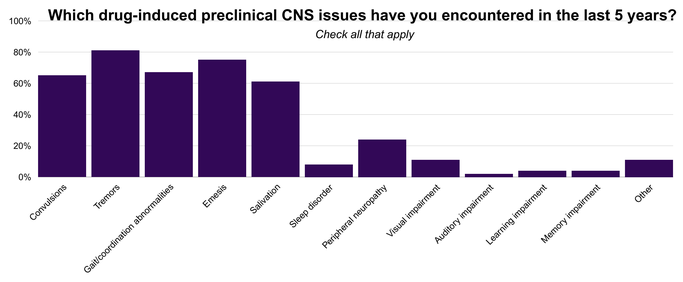
Majority of participants across surveys described their current:

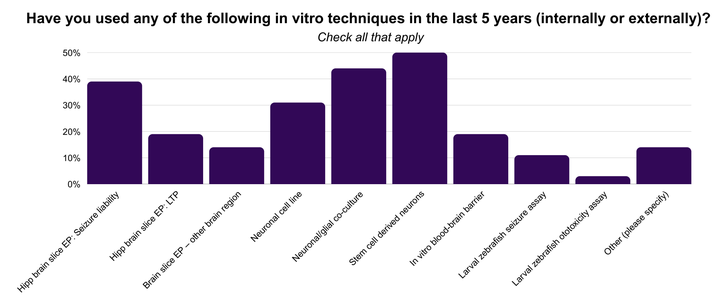
- Position as "Toxicologist"
- Company/institution as having >1000 employees

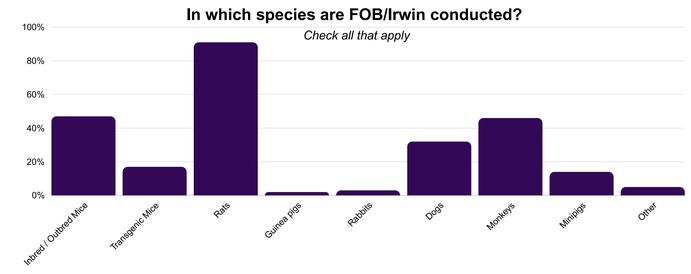


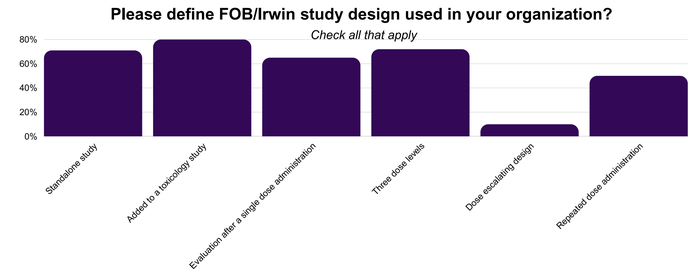
*Due to limited poster space, select data from the survey are presented here.

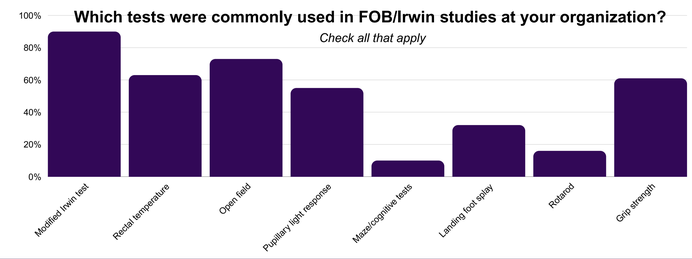
Central CNS



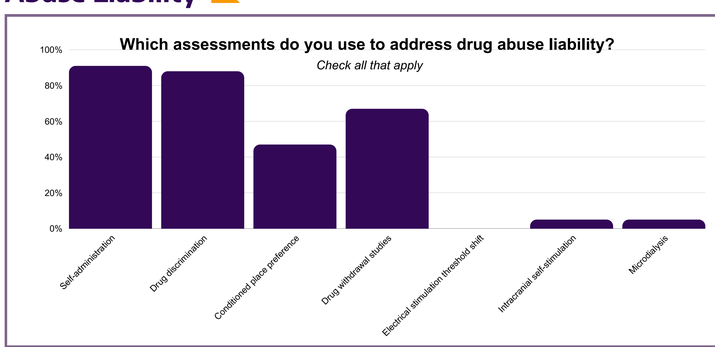




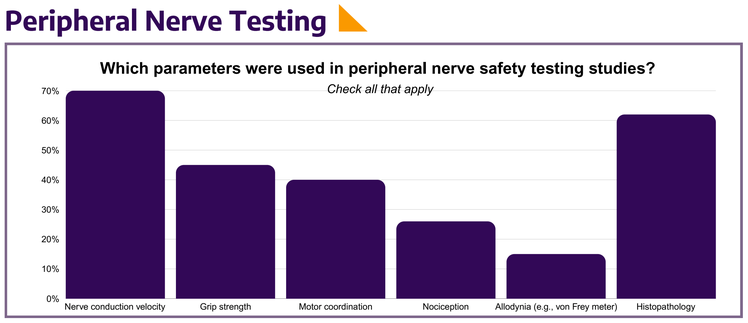




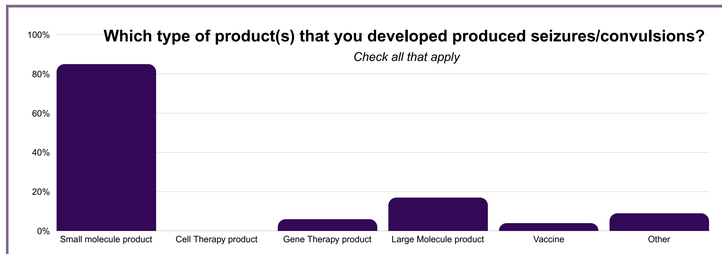
Abuse Liability

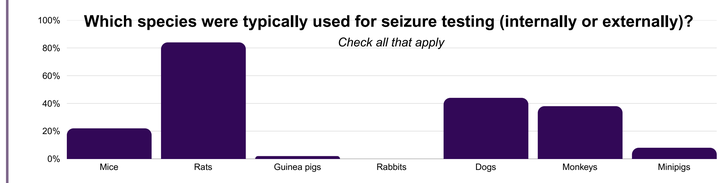


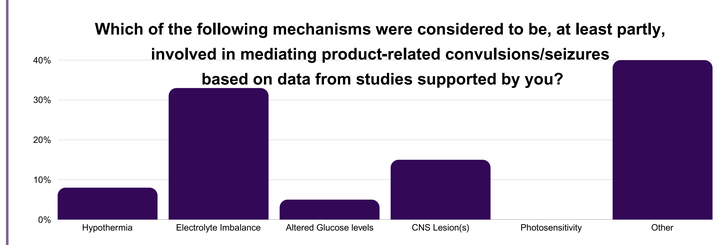
Peripheral Nerve Testing

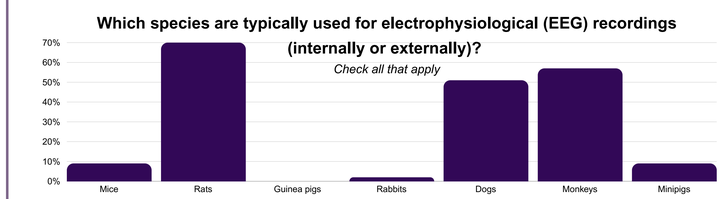


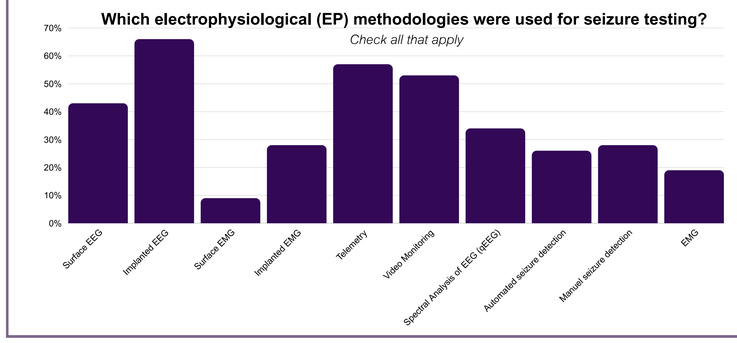
Seizure Liability











Conclusions

- Key differences observed in the demographic profile for the 2024 and 2015 surveys
  - Fewer respondents in 2024 vs. 2015
  - Fewer respondents from Asia in 2024 vs. 2015
- Various severe CNS issues were encountered by respondents when conducting preclinical and clinical studies – e.g., convulsions and gait/coordination abnormalities
- Numerous in vitro and in vivo assays were reportedly used by respondents to evaluate CNS hazards such as:
  - Seizures
  - Ototoxicity
  - Abuse liability
  - Peripheral Nerve damage
- Assays reported by respondents employed a variety of endpoints and other design features, likely related to factors that include:
  - Species tested
  - Product pharmacological/toxicological profile
  - Clinical dose schedule mimicked
- CNS issues reported were due to altering various factors:
  - Anatomy/Physiology
  - On/off target effects
  - Experimental procedures

References

Authier S., Arezzo, J., **Delatte M.S.**, *Kallman, M.J., Markgraf, C., Paquette D., Pugsley M.K., Ratcliffe S., Redfern W.S., Stevens J., Valentin J.P., Vargas H.M., Curtis M.J. (2016). Safety pharmacology investigations on the nervous system: An industry survey. J Pharmacol Toxicol Methods 81:37-46.*

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