

O'Callaghan, J.P.: Molecular Strategies for neurotoxicity screening: Moving beyond the one compound, one mechanism approach. Proceedings of the Conference on Alternative Toxicological Methods for the New Millennium: Science and Application, 38, 2000.

The molecular and cellular targets of neurotoxic insult are diverse and unpredictable, owing to the extreme molecular and cellular heterogeneity of the adult and developing nervous system. This neurobiological complexity constitutes the central dilemma for contemporary neurotoxicology, because any attempt to screen for neurotoxic effects associated with environmental, occupational or pharmaceutical exposures must overcome this obstacle. Current funding practices tend to favor "mechanistic" evaluations of specific chemicals/drugs/mixtures presumed to be potentially toxic to the human nervous system (e.g. metals, cholinesterase inhibitors, amphetamines, & PCBs). While such research may be invaluable for understanding neurotoxicity mechanisms associated with exposure to a particular compound or even a class of compounds, there is no reason to believe that such knowledge can be broadly applied for screening the thousands of existing and future chemicals that may pose a neurotoxic threat to humans. Indeed, given the complexity of the nervous system at all levels, it seems likely that a one compound, one mechanism of action may be the rule for neurotoxic agents, not the exception. This dictates the need for screening approaches that encompass all potential nervous system targets and mechanisms in order to provide the most effective defense against human exposures to neurotoxic agents. An understanding of, and the development of markers for, generic responses of the nervous system to neurotoxic exposures offer one avenue for screening for neurotoxic effects of broad classes of chemicals or chemical mixtures. Such responses include: glial activation (micro- and astroglial), proteolysis, neuroinflammation and generation of reactive oxygen species linked to cellular damage. Gene-expression patterns, assessed by gene-array technologies (filter or microarray), proteomics, assessed by analytical mass spectrometry, and toxicant-induced cell-signaling, assessed by phospho-state-specific antibodies linked to gene transcription, offer the potential for detection and characterization of novel markers of neural injury associated with the above-mentioned neurotoxic responses. Developing a data base of novel neural injury markers using these techniques can provide a molecular and cellular basis for interpreting and validating data obtained with emerging noninvasive imaging technologies. In so doing, a rapid, inexpensive, imaging-based approach to neurotoxicity assessment can be implemented with an associated reduction in animal usage.