Discuss the main types of end point used in toxicity testing in cellular system ,...

Science, Biology

Non-animal Methods for Toxi Testing Toxi screening for the myriad of compounds developed and released annually to the public has come a longway since the concept has been developed. For a much longer time animal models were mostly used in these screenings due to their short lifespans and quicker response to the toxic substances, which are easier to observe in comparison with human subjects (Sass, 2000). However, in recent years there has been a considerable increase in pressure of developing toxicity tests that bear greater semblance to human cellular systems due to rising issues in using animals such as the humane treatment of animals, the costs for maintaining and breeding the test animals, related problems such as incompatibility with human cellular systems (i. e. inbreeding of animals, gender/species differences, in turn causing differences in pharmacologic or toxin mode of actions), unrealistic dosages of toxins, small test populations, inefficiencies in obtaining sound results and the lack of other human factors such as diseases in the test subjects (Knight, 2008, p. 214). The combination of inefficiencies and expenses that occur as the result of the need to comply with toxicity tests cause the release of chemicals that had little to no proper toxicity tests, and can be potentially lethal to users (Rotroff, et al., 2010). As a result, other non-animal solutions were developed, which use mostly cells and cultures in vitro, and in turn can expect faster results that better resemble human cellular processes (Andersen and Krewski, 2009). Despite these outlooks, other setbacks in the use of alternative methods of toxicity testing can still occur such as optimisation and standardisation of methods, validation of the results, and the relative expenses of performing only small

to medium loads in assays especially with regards to automated processes such as sampling and readings (Wetmore, et al. 2012). Still, the use of cell lines in cell-based toxicity screening assays seem promising through the use of in vitro tests with increased loads in assay while using viable cells such as primary cells, immortalised cell lines, human cells and stem cell-derived systems, and these can improve both outcome paces and predictive value of the tests in relation to human cell system toxicity (Basketter, et al., 2012; Riss and Moravec, 2004). A point to consider when opting for cell-based toxicity assays is the expected endpoints of the tests, which are dependent on the objectives of the test, whether these tests are cost-effective, if the tests can provide high throughput results, the degree of uniformity needed in the cell assays, and reliability or reproducibility of the results (Judson, et al., 2013). For example, there are some assays which use viable cell counts to determine toxicity of chemicals, such as the use of basal cell culture for in vitro cytotoxicity tests. These tests determine cytotoxicity in chemicals without any information yet, and as such can be used to rank them in terms of potential toxicity based on observed cell deaths (Ekwall, et al., 1990). Because these tests mostly rely on cell counts and finding out the viability of the cells, results can be gathered in shorter time in comparison with other kinds of tests. In addition, the results can be predicted based on the known chemical structures of the chemical, and thus it can also be used as a confirmatory test. However because there has been much greater emphasis on biochemical pathways of toxic chemicals, establishing the lowest amount that could possibly cause cellular events and how these chemicals affect

reproductive and developmental processes, the use of cytotoxicity has been determined to be insufficient in establishing chemical dosage rates(Basketter, et al., 2012, p. 18). Another example of an in vitro assay that relies on primary cell lines, using neurotoxicity as an endpoint is the development of central nervous system (CNS) tissues using proliferation assays to observe cellular interactions and how neurotoxicity occurs (van Liet, 2010, p. 20). While there were developments and ease in observing how metals and pesticides can affect neurodevelopment and chemical signalling among cells within a CNS system, using this assay itself has proven to be rather tedious due to the complexities in culturing CNS tissues, uniformity of cellular responses and the need for additional tests to find out whether or not aggregated cultures can provide similar results to monolayer cells (Basketter, et al., 2012). These issues can affect the outcome of toxicity assays using CNS cells, and unless standardisation of methods can be done this kind of assay may not be as cost-effective among other toxicity assays. Lastly, in vitro metabolic assays such as hepatocellular metabolism with organ toxicity as endpoint are used, using factors such as liver blood flow, association and dissociation rates of chemicals to plasma proteins, kinetics of hepatocellular uptake and metabolism of the chemical in question. These must first be identified before proceeding to toxicity tests in order to take into account in vivo absorption rates of the chemical along with other factors that can affect dosage response such as the composition of the culture media and how the chemical binds to surfaces, thereby increasing the efficiency of the test (Basketter, et al., 2012, p. 216). However because liver

cells produce relatively similar results in toxicity tests and in turn allows predictability of metabolism and pharmacokinetic mechanisms, hepatocellular metabolism assays are considered to be cost-efficient and are thus good endpoints for assessing chemical toxicity. The use of in vitro methods in using cell-based toxicity assays seem promising due to faster results compared with using animal in vivo cells, and in turn the results of such tests have greater semblance to how these potential toxic substances can affect the human body. But in order to increase cost-effectiveness of these in vitro tests considerations such as test objectives, endpoints used, standardisation of methods and validation procedures must be taken into account in order to perform tests suitable to needs. This is because cell lines, especially undifferentiated cells may have variability in terms of proliferation and growth even without the addition of the chemicals, and without such prior knowledge false-negatives or false-positives can arise, leading to inaccuracies with the labelling of the chemicals. Despite these issues, the use of such methods can remove issues from the use of animal models such as incompatibility with human cellular systems, inhumane treatment of test animals, costs in breeding and maintenance, lack of additional disease factors, size of test populations, etc., which contribute to lesser toxicity assays of chemicals and in turn increases the number of potentially lethal products in the market. Because of the health impact of the lack of proper toxicity measurements for the growing number of synthesised compounds annually, there has been an increase in the lobbying and pressuring in the usage of human cell lines in toxicity assays, which entails agencies to work

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