Toxicity Testing In Vitro: Regulatory Aspects

12

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Contents

Abstract

In vitro testing in toxicology was limited for a long time to testing for possible genotoxic properties of a substance. Cell or tissue culture methods are now used for the early toxicological assessment of new substances within the context of screening tests and for mechanistic investigations. In this respect, in vitro methods represent a valuable adjunct to animal studies, without being able to replace animal studies completely at the present time. New developments in the area of microphysiological systems (MPS) suggest that in specific cases like the development of biologics as pharmaceuticals, where relevant animal models are not available due to the human-specific nature of the biologic, but also for improved mechanistic evaluations, human in vitro models will be required or at least deliver helpful information.

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Introduction

"In vitro" tests are known colloquially as "test tube experiments," i.e., they are performed outside the living organism. According to this definition, in vitro testing encompasses tests with isolated organs or tissues, cells, cell organelles, receptors, or ion channels. The culture of cells from different organs is the in vitro method most commonly used in toxicology, with a distinction being made between *primary cell cultures* and permanent *cell lines*. Primary cell cultures are prepared from freshly isolated cells obtained during a necropsy or from surgical specimens, for example. Permanent cell lines, such as tumor cell lines, are obtained from cells which have been transformed spontaneously or in a targeted manner such that they can be passaged without limit and kept in stock. They can now be acquired easily from cell banks. Another source for human cells is stem cells. *Adult stem cells* are isolated from donor fetal or adult tissue(s), whereas *pluripotent stem cells* can be isolated from the inner cell mass of the blastocyst, as with *embryonic stem (ES)* cells, or through nuclear reprogramming, as with induced pluripotent stem cells (iPSC). Which culture systems should be used must be decided individually, depending on the specific parameter(s) being studied.

With regard to their aims, in vitro tests can be viewed in two ways: firstly, as a method of screening and, secondly, in the context of *mechanistic evaluation*. Whereas pharmacological research has been making use of cell and tissue cultures for a long time in efficacy testing of new medicinal products, the use of such systems in toxicology was previously limited to just a few areas of investigation. In vitro methods now represent a vital tool in the early toxicological characterization of new substances, however. This can be attributed, using pharmaceutical research as an example, to the significant increase in efficiency (higher output) and the resulting need to subject potential candidates for development to toxicological assessment at an early stage and to support optimization. It is clear that, because of their low throughput and the large amounts of substance required, conventional toxicological methods, and animal studies in particular, are not able to meet the requirements placed on screening. In vitro methods, on the other hand, have low substance requirements; they can be performed quickly and they are in many cases cheaper. The relatively simple in vitro systems do, however, often show limitations when it comes to generating data on a substance about which little or no previous information exists. This kind of information can usually be provided only by methods with a high level of complexity, which naturally cannot be achieved with simple in vitro methods used for screening. The particular value of in vitro methods therefore lies in the investigation of questions arising on the basis of specific evidence from an

animal study. In this connection, early screening must always be seen as *screening via knowledge*, i.e., based on previous information. Once a data pool generated under in vivo conditions is available, this can be examined in detail with the aid of cell or tissue culture methods. Another particular benefit of in vitro methods lies in the fact that human material (such as surgical specimens) can be used, and the basis for human risk assessment can thus be improved. In vitro methods can therefore represent a useful adjunct to animal studies with the possibility of evaluation of the human relevance of findings obtained in animals.

Possible uses of established in vitro screening models are the following:

- Detection of cellular toxicity in defined organ models
- Testing for specific toxicity (e.g., phototoxicity)
- Tests using receptors or ion channels in the context of safety pharmacology studies
- Genotoxicity testing

Some of the currently common in vitro methods and their possible uses are described below. New developments in the area of MPS which strive for in vivo-like complexity will be described in a separate chapter.

Tests with Liver Cell Cultures (Biotransformation and Cytotoxicity)

The liver plays a central role in the metabolism of foreign substances. Its extraordinary capacity to convert and break down substances is largely attributable to the parenchymal cells of the liver or hepatocytes. From a toxicological point of view, the liver is one of the most important target organs for toxicity. It is therefore not surprising that, in the context of in vitro testing, particularly great importance is attached to tests using isolated liver cells. Hepatocytes from the common study animal species (mouse, rat, dog, or monkey) are relatively easy to obtain because most toxicological studies end with necropsy of the animals. Obtaining human tissue is more difficult, and use must be made here of surgical specimens obtained, for example, from resected liver tissue, following tumor surgery. The hepatocytes obtained at necropsy or from surgical specimens via perfusion are used as primary cultures. They can be maintained in culture for days to a few weeks depending on the culture method, but lose their full functionality over time, with a particularly sharp decline in their cytochrome P450 enzyme (CYP) activity. The use of newer culture methods such as sandwich culture, in which primary hepatocytes are sandwiched between layers of a collagen matrix or cultured as 3D spheroids, potentially as a coculture with non-parenchymatous liver cells, significantly prolongs the period for which metabolic activity can be maintained. Under these conditions, it is possible to maintain hepatocytes in culture for up to 14 days with rather stable basal and inducible CYP metabolic activity, although at a likely lower level than in vivo (Gómez-Lechón et al. 2014).

Tests on the metabolism and cytotoxicity of substances can be performed with liver cells obtained and maintained in culture in this way. Preliminary statements can thus be made about their biotransformation without animal studies or trials in humans having been conducted. Within the context of drug development, these tests are therefore also of particular importance because the results obtained in human hepatocytes can be compared with the results from the hepatocytes of the study animal species in which the toxicological studies have been or should be carried out. On the basis of the comparability of the metabolic pattern (human compared with animal in vitro), conclusions can then be drawn as to whether the study animal species used in the toxicological studies can be classified as relevant in terms of their applicability to humans.

Cytotoxicity tests with liver cells involve measuring the levels of certain enzymes in the culture supernatant. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) can be mentioned here as examples. Increased levels of these (cellular) enzymes in the supernatant are an indicator of cell damage, following the same principle as is applied in the diagnosis of liver damage in patients (increased levels of liver-specific enzymes in the blood as an indicator of liver damage). Determination of mitochondrial dehydrogenase activity (e.g., with the MTT assay) allows to assess the effect of a compound on the metabolic activity of hepatocytes, which essentially correlates with the level of viable cells in an incubation. The use of liver cell cultures in the context of early screening has proven particularly effective when previous information is available from in vivo studies. Under these conditions ("screening via knowledge"), tests with hepatocytes can be used for further chemical optimization with a view to avoiding or eliminating hepatotoxic properties in a new substance. Inconclusive findings from animal studies or significant species differences resulting in uncertainty in assessing the possible risk to humans provide the basis for another possible use. In these cases, testing with human specimens can improve the basis for the risk assessment. Although tests with liver cell cultures are not a regulatory requirement, they represent an important internal decision-making criterion in the context of substance preselection or supplementing/supporting in vivo data with regard to their applicability to humans.

Tests with Mouse Fibroblasts (Phototoxicity)

The term "phototoxicity" is used to refer to reactions triggered when an organism exposed to light or the sun shows particular sensitivity to certain (phototoxic) substances, resulting in harmful health effects. These kinds of reactions can range from local symptoms resembling sunburn (redness) to severe burns (extensive skin necrosis) and general health effects. A large number of substances (especially cosmetics, medicinal products) are now known to have phototoxic potential. It is therefore appropriate that the legislation requires manufacturers to provide information on phototoxicity in the presence of relevant grounds for suspicion (photo instability, presence/accumulation of the substance in the skin) or for certain indications (dermally applied substances). Traditionally, these kinds of tests were

performed in animals and involved mice, rats, guinea pigs, or rabbits being irradiated with UV light after being treated with the substances to be tested.

The most widely used in vitro assay for phototoxicity is the "in vitro 3T3 Neutral Red Uptake Phototoxicity Test" (3T3 NRU-PT) for which a guideline (OECD 2004) is available, which has recently been updated (OECD 2019). The assay was developed under the leadership of the Center for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET) of the Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV). It is performed using a permanent mouse fibroblast cell line (Balb/c 3T3) and is based on the testing and comparison of the cytotoxic effects of a substance in the presence or absence of exposure to UV light. This in vitro assay is also part of a sequential phototoxicity testing strategy proposed in a CPMP guidance document (CPMP/SWP/398/01 2002), and it is also mentioned in an ICH guideline for the testing of pharmaceutical drugs (CHMP/ICH/752211/2012 2015). While it is acknowledged that the 3T3 NRU-PT assay is a very sensitive test and many positive findings are not confirmed in in vivo follow-up studies, the importance of the 3T3 NRU-PT assay within the context of a sequential testing strategy lies in the fact that if a negative result is obtained, i.e., if evidence is obtained of the absence of phototoxicity, no other tests, and specifically no animal studies, need to be performed, something which is to be greatly welcomed from the point of view of limiting the number of animal studies. However, a positive result in the 3T3 NRU-PT should not be regarded as indicative of a likely clinical phototoxic risk, since it is primarily a hazard identification test. Even in the case of a positive in vitro phototoxicity test, the concentration at which cytotoxicity is observed in vitro after UV irradiation can be used for calculation of safety margin in the context of expected human blood concentrations at therapeutic dose levels.

Tests with Isolated Ion Channels (Cardiotoxicity, ECG Changes)

In the context of the risk assessment of medicinal products, possible cardiotoxic properties, particularly in medicinal products used primarily in non-cardiovascular indications, have been the focus of attention for some time now. The properties concerned are characteristic ECG changes (prolongation of the QT interval as evidence of delayed cardiac repolarization) which are considered predictive in respect of the induction of arrhythmias. This kind of potential must be identified at an early, i.e., preclinical, stage, and the legislation therefore consistently requires appropriate nonclinical (safety pharmacology) studies. Reference should be made in this connection to an ICH test guideline entitled "The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals" (CPMP/ICH/423/02 2005). Among the tests stipulated in this test guideline are tests using human potassium channels which are expressed in a cell line in a stable manner (hERG). The background for the tests is the fact that cardiac repolarization is essentially mediated by potassium flow and that drug-induced inhibition of the ion channels leads to prolongation of the action potential, which

makes itself apparent in the ECG in the form of prolongation of the QT interval. Tests using hERG channels represent an additional and new example of in vitro studies that are established in regulatory terms. Enhanced evaluation of pro-arrhythmic risk is now being conducted by international initiatives including the Comprehensive in vitro Proarrhythmia Assay (CiPA) and the Japanese iPS cardiac safety assessment initiatives (Kanda et al. 2018; Blinova et al. 2018). The CiPA approach is based on several key modalities including (1) testing of further major ion channels in addition to hERG in correspondingly transfected cell lines, (2) in silico modeling of the ion channel effects, (3) proarrhythmic assessment in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), and (4) clinical assessment of electrocardiograms from phase I human studies.

Most recent developments in in vitro cardiotoxicity testing expand the use of hiPSC-CM, by testing not only for proarrhythmic risk but also for other relevant parameters like compound-induced effects on changes in contractility, voltage, and/or Ca handling of cardiomyocytes (Saleem et al. 2020).

Tests with Mammalian Cell Cultures (Genotoxicity)

In vitro methods are already long established and stipulated by test guidelines as standard in the field of genotoxicity testing. These kinds of test were in fact already in use even before the development and use of in vivo methods. For the testing of a substance for genotoxic properties, it is assumed that no single test system is capable of predicting a possible risk to humans in a reliable manner. This is why batteries of tests are used to test substances for possible genotoxic effects. A typical battery of tests, stipulated for the testing of medicinal products, for example, consists of two in vitro tests (gene mutation test in bacteria, chromosomal aberration test in mammalian cell cultures) and one in vivo test (micronucleus test in the bone marrow) (Galloway 2017). To perform chromosomal aberration tests under in vitro conditions, cells in culture are treated with the substance to be tested in both the presence and absence of external metabolic activation, arrested at metaphase by administration of a spindle inhibitor, fixed, and then evaluated under the microscope. Permanent fibroblast cells originating from various Chinese hamster tissues are most often used for these tests, including V79, CHO, or CHL cells. These are particularly suitable for chromosome analyses because of their small number of chromosomes and especially their uncomplicated karyotype. Human peripheral lymphocytes are also used.

Tests with Incubated Chicken Eggs (Various Parameters)

Incubated chicken eggs have long been a well-established test system in biomedical research. Development stages without any sensitivity to pain are also used as a model. Both the embryo and the extraembryonic vascular systems are considered as target structures. The substances to be tested are administered directly or via the

intravascular route. Functional and/or morphological parameters are end points. The results of numerous studies show that incubated chicken eggs are used to determine the irritation potential; to screen for cardiovascular effects, phototoxicity, and angiogenesis; and in cancer research. More recently and since in vitro cell culture tests have been developed for these toxicities, testing with incubated chicken eggs is being used less frequently, especially for skin and eye irritation.

Human Embryonic Stem (hES) Cells for Use in Toxicity Testing, E.g., Early Development Toxicity Testing

Early developmental toxicity assays for screening of various compounds for the potential risks for abnormal development in the growing embryo have been traditionally based on animal cells. As species differences might affect the accuracy of the assessments, there is an increasing need for alternative cell sources. In vitro differentiation of hES cells bears a resemblance to the early stages of human embryonic development and offers in principle the possibilities for alternative toxicity testing.

Developmental toxicity evaluations, as used in safety assessment assays, are sometimes suffering from a lack of normal, reproducible, and easily available human cell systems. In this context, pluripotent hES cells and their derivatives have the potential to improve the quality of targets, hits, and leads, thus reducing late-stage attrition. The promise of hES cells for in vitro toxicology is the indefinite access to starting material of identical origin in combination with highly human-relevant assays for, e.g., developmental toxicity testing (Luz and Tokar 2018). Very recently such developmental toxicity testing in stem cells has been evaluated in hiPSC, which yielded promising results with a list of relevant reference compounds (Aikawa 2020).

Possibilities and Limitations of Established In Vitro Toxicity Testing

It is no longer possible to imagine modern toxicity testing without in vitro test systems. They enable initial information on toxicological properties to be obtained within the context of early screening and can provide chemical research with important indications with regard to the possibilities for optimization. The reliability of such screening is enhanced considerably if previous information is already available on the substance ("screening via knowledge"). Mechanistic investigations represent a second focus of in vitro methods. The same principle applies here as with "screening via knowledge," i.e., that the real role of in vitro methods lies in the targeted investigation of specific questions based on previous information obtained from in vivo studies. In vitro methods can add major value, however, e.g., by making it possible for tests to be carried out using human specimens, and thus improve the basis for the risk assessment. Quantitative assessments aimed at extrapolating concentrations from in vitro tests to the in vivo situation (doses) are problematic. It is therefore not surprising that the in vitro test systems established so far for

regulatory purposes (e.g., in vitro genotoxicity, phototoxicity, or cardiotoxicity testing) are almost always part of an integrated battery of in vitro/in vivo tests, and the results of in vitro testing are assessed in the sense of a yes/no answer and not in terms of a quantitative assessment of the risk.

New Developments: Microphysiological Systems (MPS)

To overcome some of the limitations of simple 2D culture systems, several approaches are being pursued to make in vitro models more in vivo-like. From simple to more and more advanced, this includes the following:

1. 2D cell lines in static culture condition representing mostly dedifferentiated cells, i.e., most current screening systems
2. Primary cells in static culture which are associated with some in vivo functionality like CYP enzyme activity in the case of primary hepatocytes and which can be improved with (a) extracellular matrices (ECM), e.g., the hepatocyte sandwich model for shorter-term studies, or (b) co-culture of two cell types, e.g., so-called micro-patterned liver models containing hepatocyte and fibroblasts (Khetani et al. 2015)
3. 3D spheroids either in static culture or in a microfluidics system for at least 2 weeks use (Messner et al. 2013)
4. 3D organoids generated by seeding stem or progenitor cells into an ECM, which then differentiate into different cell types and arrange themselves into organ-like structures (Kretzschmar and Clevers 2016)
5. Microfluidic models for longer-term studies in which microfluidic flow mimics in vivo blood flow and shear stress (Marx et al. 2020; Fabre et al. 2020)
6. 3D-bioprinted models whose major goal is to reach an in vivo-like organ structure with the possibility to print blood vessels and which can be kept in either static or microfluidic modes (Mota et al. 2020)

Currently there is no consensus yet about the exact definition of MPS. Sometimes 3D spheroids or static co-cultures of at least two cell types are counted as MPS, that is, any culture design beyond simple 2D. In a narrower sense, an MPS should be composed of several cell types organized into an in vivo-like structure within a relevant ECM and equipped with flow or other mechanical cues. More advanced systems may contain immune system components.

For MPS models to be useful in preclinical testing and to allow better assessment of potential human safety issues than simple cell line models, they need to contain relevant cell types and should be evaluated for characteristic function of the organ they are supposed to model, including expected responses to a list of reference agents. Specific guidance is given for major organs like the liver (Baudy et al. 2020), lung (Ainslie et al. 2019), kidney (Phillips et al. 2020), and gastrointestinal tract (Peters et al. 2020). In the case of the liver, a recent example showed that it is possible to reproduce species-specific toxicities in an MPS format (Jang et al. 2019). Microfluidics systems also allow to combine different organ models in an in vivo-like circuit, which are called body-on-a-chip systems. With a liver-heart-on-a-chip

system with both hepatocytes and cardiomyocytes derived from the same hiPSC line, a clinically relevant drug-drug interaction could be modeled, in which inhibition of biotransformation of an arrhythmogenic to a non-arrhythmogenic drug in the liver MPS leads to arrhythmia induction in the downstream cardiac MPS (https://www.biorxiv.org/content/10.1101/2020.05.24.112771v2).

A challenge for many advanced models, especially of more elaborate 3D structures, is the introduction of blood vessels to allow supply of oxygen and nutrients in an in vivo-like manner. With 3D bioprinting such vessel structures can be integrated into organ models, as reported for a heart model which allowed the printing of contracting cardiac patches and of thicker vascularized tissues (Noor et al. 2019). To be able to print whole organs, this technology must still overcome many challenges, from recreation of the in vivo blood vessel network to producing sufficient amounts of mature cells. But even such small patches which can be printed already may be used for safety testing or developed toward disease models.

Cross-References

- ▶ Examination of Organ Toxicity
- ▶ Importance of Xenobiotic Metabolism: Mechanistic Considerations Relevant for Regulation
- ▶ Integration of Advanced Technologies into Regulatory Toxicology
- ▶ International Regulation of Toxicological Test Procedures
- ▶ Omics in Toxicology
- ▶ Specific Toxicity Tests for Neurotoxicity, Immunotoxicity, Allergy, Irritation, Reprotoxicity, and Carcinogenicity
- ▶ Toxicodynamic Tests

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