問題を閲覧する

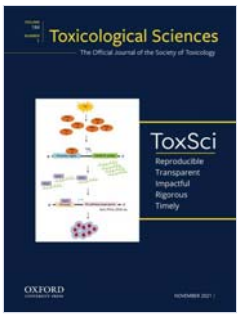
年

2021年

問題

184巻、1号、2021年11月、1〜182ページ

ボリュームで閲覧



184巻、1号
2021年11月
表紙画像

ISSN 1096-6080
EISSN 1096-0929

<前

184巻、1号、2021年11月

バイオマーカー

肺がんドライバーの突然変異のCarcSeq測定を使用したクローン拡大の評価および自発性肺腫瘍のマウス系統および性関連発生率との相関

ケリー・L・ハリス、カレン・Lマッキム、ミーガンBマイヤーズ、Binsheng功、ジョシュア徐 ...

Toxicological Sciences、第184巻、第1号、2021年11月、1〜14ページ、
https：//doi.org/10.1093/toxsci/kfab098

概要 ▲

自発的に発生する癌ドライバー変異（CDM）のレベルの変動の定量化は、クローンの拡大を評価し、新生物の発生の将来のリスクを予測するために開発されました。具体的には、エラー訂正された次世代シーケンシング法であるCarcSeqとマウスCarcSeqパネル（ヒトおよびラットのパネルに類似）が開発され、ホットスポットCDMが豊富なアンプリコンのパネルで低頻度の変異を定量化するために使用されました。パネルアンプリ

コンのサブセットにおける突然変異の*Braf*、*EGFR*、*Kras*の、*STK11*、および*TP53*、2年後の肺腫瘍の発生率に関連していた。これは、16週齢の男性と女性、B6C3F1およびCD-1マウス（10匹のマウス/性別/系統）の肺DNAで測定された全体の中央値変異画分（MF）からの中央絶対偏差（MAD）を相関させることによって達成されました。バイオアッセイ対照群で報告された自発性肺胞/気管支肺胞腺腫および癌腫の割合。MFが1×10^{-4}を超える合計1586匹のマウス肺変異体回収されました。非同義変異と同義変異の比率を使用して、正の選択的利点をもたらす回復した変異の割合を評価しました。最大の比率は、調べた中で最も肺腫瘍に敏感なモデルと考えられているオスのB6C3F1マウスで観察されました。回復した再発性の非同義マウス変異のうち、55.5%がヒト腫瘍で報告されており、その多くはヒト癌ホットスポットコドンに相当するマウス内またはその周辺に位置しています。正常なヒト肺DNAサンプルで測定されたアンプリコンの同じサブセットのMADは、中程度の強度と境界線の有意性と年齢（がんの危険因子）、および加齢に伴う累積肺がんリスクとの相関を示し、MADが種の推定に役立つ可能性があることを示唆しています。

記事を見る　補足データ

発がん

クララ細胞は、ペルメトリン誘発性のマウス肺腫瘍形成の主要な標的です🛒

緒方恵子、劉楊、大原綾子、川本健介、近藤美和 ...。

Toxicological Sciences、第184巻、第1号、2021年11月、15〜32ページ、https：//doi.org/10.1093/toxsci/kfab103

概要 ▲

ペルメトリンは、雌のCD-1マウスでは肺腺腫を増加させることが示されていますが、雄のマウスやWistarラットでは増加しません。ペルメトリン誘発雌マウス肺腫瘍形成のために提案された作用機序（MOA）には、クララ細胞の形態学的変化が含まれます。クララ細胞増殖の増加; クララ細胞過形成の増加、および肺腫瘍形成。この研究では、雌のCD-1マウスを腫瘍形成用量（2500および5000 ppm）のペルメトリンで14日間および/または28日間、非腫瘍形成用量（20 ppm）で処理すると、クララ細胞の複製DNA合成が増加しました。雌マウスの肺サンプルのグローバルな遺伝子発現分析は、ペルメトリン処理が細胞増殖

に関連する3つの遺伝子、すなわちアルデヒドデヒドロゲナーゼ*3a1*（*Aldh3a1*）、酸化ストレス誘発性増殖阻害剤*1*、およびチオレドキシンレダクターゼ*1*。20ppmではなく2500および5000ppmのペルメトリンで7日間処理すると、これら3つの遺伝子のmRNAレベルが大幅に増加しました。免疫組織化学的分析は、クララ細胞分泌タンパク質、CYP2F2、およびALDH3A1がクララ細胞に共局在することを示しました。細胞増殖マーカーとしてKI67を使用した肺細胞のフローサイトメトリー分析によって確認されました。全体として、現在のデータは、クララ細胞が雌マウスの肺におけるペルメトリン投与の主要な初期標的であることを実証することにより、提案されたMOAを拡張します。ヒトは、マウスのクララ細胞増殖と肺腫瘍形成を増加させる薬剤に対して量的にはるかに感受性が低いため、ペルメトリンがヒトの肺腫瘍を生成できなかった可能性が最も高いです。この結論は、いくつかの研究から入手可能な否定的な疫学データによって裏付けられています。

記事を見る　Supplementary data

LncRNA DUXAP10 Upregulation and the Hedgehog Pathway Activation Are Critically Involved in Chronic Cadmium Exposure-Induced Cancer Stem Cell-Like Property

Hsuan-Pei Lin, Zhishan Wang, Chengfeng Yang

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 33–45, https://doi.org/10.1093/toxsci/kfab099

Abstract ▲

Cadmium (Cd) is a well-known lung carcinogen. However, the mechanism of Cd carcinogenesis remains to be clearly defined. Cd has been shown to act as a weak mutagen, suggesting that it may exert tumorigenic effect through nongenotoxic ways, such as epigenetic mechanisms. Long noncoding RNAs (lncRNAs) refer to RNA molecules that are longer than 200 nucleotides in length but lack protein-coding capacities. Regulation of gene expressions by lncRNAs is considered as one of important epigenetic mechanisms. The goal of this study is to investigate the mechanism of Cd carcinogenesis focusing on the role of lncRNA dysregulations. Cd-induced malignant transformation of human bronchial epithelia BEAS-2B

cells was accomplished by a 9-month low-dose Cd ($CdCl_2$, 2.5 μM) exposure. The Cd-exposed cells formed significantly more colonies in soft agar, displayed cancer stem cell (CSC)-like property, and formed tumors in nude mice. Mechanistically, chronic low-dose Cd exposure did not cause significant genotoxic effects but dysregulated lncRNA expressions. Further Q-PCR analysis confirmed the significant upregulation of the oncogenic lncRNA DUXAP10 in Cd-transformed cells. DUXAP10 knockdown in Cd-transformed cells significantly reduced their CSC-like property. Further mechanistic studies showed that the Hedgehog pathway is activated in Cd-transformed cells and inhibition of this pathway reduces Cd-induced CSC-like property. DUXAP10 knockdown caused the Hedgehog pathway inactivation in Cd-transformed cells. Furthermore, Pax6 expression was upregulated in Cd-transformed cells and Pax6 knockdown significantly reduced their DUXAP10 levels and CSC-like property. In summary, these findings suggest that the lncRNA DUXAP10 upregulation may play an important role in Cd carcinogenesis.

View article Supplementary data

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY

FEATURED

Iodoacetic Acid, a Water Disinfection Byproduct, Disrupts Hypothalamic, and Pituitary Reproductive Regulatory Factors and Induces Toxicity in the Female Pituitary FREE

Rachel V L Gonzalez, Karen E Weis, Andressa V Gonsioroski, Jodi A Flaws, Lori T Raetzman

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 46–56, https://doi.org/10.1093/toxsci/kfab106

Abstract ▲

Iodoacetic acid (IAA) is a water disinfection byproduct (DBP) formed by reactions between oxidizing disinfectants and iodide. *In vitro* studies have indicated that IAA is one of the most cyto- and genotoxic DBPs. In

humans, DBPs have been epidemiologically associated with reproductive dysfunction. In mouse ovarian culture, IAA exposure significantly inhibits antral follicle growth and reduces estradiol production. Despite this evidence, little is known about the effects of IAA on the other components of the reproductive axis: the hypothalamus and pituitary. We tested the hypothesis that IAA disrupts expression of key neuroendocrine factors and directly induces cell damage in the mouse pituitary. We exposed adult female mice to IAA in drinking water *in vivo* and found 0.5 and 10 mg/l IAA concentrations lead to significantly increased mRNA levels of kisspeptin (*Kiss1*) in the arcuate nucleus although not affecting *Kiss1* in the anteroventral periventricular nucleus. Both 10 mg/l IAA exposure *in vivo* and 20 μM IAA *in vitro* reduced follicle stimulating hormone (FSHβ)-positive cell number and *Fshb* mRNA expression. IAA did not alter luteinizing hormone (LHβ) expression *in vivo* although exposure to 20 μM IAA decreased expression of *Lhb* and glycoprotein hormones, alpha subunit (*Cga*) mRNA *in vitro.* IAA also had toxic effects in the pituitary, inducing DNA damage and P21/*Cdkn1a* expression *in vitro* (20 μM IAA) and DNA damage and *Cdkn1a* expression *in vivo* (500 mg/l). These data implicate IAA as a hypothalamic-pituitary-gonadal axis toxicant and suggest the pituitary is directly affected by IAA exposure.

View article

Temephos Decreases Sperm Quality and Fertilization Rate and Is Metabolized in Rat Reproductive Tissues at Low-Dose Exposure

Ángel Ramos-Flores, Israel Camacho-Hernández, Adolfo Sierra-Santoyo, María de Jesús Solís-Heredia, Francisco Alberto Verdín-Betancourt ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 57–66, https://doi.org/10.1093/toxsci/kfab100

Abstract ▲

Temephos is an organophosphorus pesticide used in control campaigns against vectors that transmit diseases, including dengue, a public health concern. The WHO

classifies temephos in category III and its safe concentration (low-observable-adverse-effect level) in male rats is 100 mg/kg/day for up to 44 days. Temephos inhibits acetylcholinesterase (AChE) and is metabolized in different tissues, probably by mixed-function oxidases; one of its metabolites is bisphenol S (BPS), which is considered an endocrine disruptor. The aim of this study was to evaluate the effects of temephos on sperm function and its biotransformation in the testis, epididymis, and other tissues to explore its toxicity in rats treated with 100 mg/kg/day/5 or 7 days (gavage). AChE activity was inhibited 70% starting on day 3 and 13 or 41% mortality was observed at 5 or 7 days, respectively. After 7 days, temephos significantly decreased sperm motility (30%) and viability (10%) and increased (10%) lipoperoxidation, and the sperm DNA exhibited no damage. Temephos was distributed and metabolized in all tissues, with the highest levels observed in the adipose tissue and temephos levels were 16-fold higher in the epididymis than in the testis. Notably, BPS was observed in the testis. At 5 days, decreased sperm motility (12.5%) and viability (5.7%) were observed and sperm fertilization decreased (30%). These results suggest that temephos decreases sperm quality and fertilization capacity at recommended safe concentrations and that it is metabolized in male reproductive tissues. This pesticide places the reproductive health of exposed people at risk, suggesting the need to reevaluate its toxicity.

View article

ENVIRONMENTAL TOXICOLOGY

Comparative Genotoxicity and Mutagenicity of Cigarette, Cigarillo, and Shisha Tobacco Products in Epithelial and Cardiac Cells

Carmen S Tellez, Daniel E Juri, Loryn M Phillips, Kieu Do, Cindy L Thomas ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 67–82, https://doi.org/10.1093/toxsci/kfab101

Abstract ▲

Epidemiology studies link cigarillos and shisha tobacco (delivered through a hookah waterpipe) to increased risk for cardiopulmonary diseases. Here we performed a comparative chemical constituent analysis between 3 cigarettes, 3 cigarillos, and 8 shisha tobacco products. The potency for genotoxicity and oxidative stress of each product's generated total particulate matter (TPM) was also assessed using immortalized oral, lung, and cardiac cell lines to represent target tissues. Levels of the carcinogenic carbonyl formaldehyde were 32- to 95-fold greater, while acrolein was similar across the shisha aerosols generated by charcoal heating compared to cigarettes and cigarillos. Electric-mediated aerosol generation dramatically increased acrolein to levels exceeding those in cigarettes and cigarillos by up to 43-fold. Equivalent cytotoxic-mediated cell death and dose response for genotoxicity through induction of mutagenicity and DNA strand breaks was seen between cigarettes and cigarillos, while minimal to no effect was observed with shisha tobacco products. In contrast, increased potency of TPM from cigarillos compared to cigarettes for inducing oxidative stress via reactive oxygen radicals and lipid peroxidation across cell lines was evident, while positivity was seen for shisha tobacco products albeit at much lower levels. Together, these studies provide new insight into the potential harmful effects of cigarillos for causing tobacco-associated diseases. The high level of carbonyls in shisha products, that in turn is impacted by the heating mechanism, reside largely in the gas phase which will distribute throughout the respiratory tract and systemic circulation to likely increase genotoxic stress.

View article Supplementary data

Neonatal Exposure to BPA, BDE-99, and PCB Produces Persistent Changes in Hepatic Transcriptome Associated With Gut Dysbiosis in Adult Mouse Livers

Joe Jongpyo Lim, Moumita Dutta, Joseph L Dempsey, Hans-Joachim Lehmler, James MacDonald ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 83–103,
https://doi.org/10.1093/toxsci/kfab104

Abstract ▲

Recent evidence suggests that complex diseases can result from early life exposure to environmental toxicants. Polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs) are persistent organic pollutants (POPs) and remain a continuing risk to human health despite being banned from production. Developmental BPA exposure mediated-adult onset of liver cancer via epigenetic reprogramming mechanisms has been identified. Here, we investigated whether the gut microbiome and liver can be persistently reprogrammed following neonatal exposure to POPs, and the associations between microbial biomarkers and disease-prone changes in the hepatic transcriptome in adulthood, compared with BPA. C57BL/6 male and female mouse pups were orally administered vehicle, BPA, BDE-99 (a breast milk-enriched PBDE congener), or the Fox River PCB mixture (PCBs), once daily for three consecutive days (postnatal days [PND] 2–4). Tissues were collected at PND5 and PND60. Among the three chemicals investigated, early life exposure to BDE-99 produced the most prominent developmental reprogramming of the gut-liver axis, including hepatic inflammatory and cancer-prone signatures. In adulthood, neonatal BDE-99 exposure resulted in a persistent increase in *Akkermansia muciniphila* throughout the intestine, accompanied by increased hepatic levels of acetate and succinate, the known products of *A. muciniphila*. In males, this was positively associated with permissive epigenetic marks H3K4me1 and H3K27, which were enriched in loci near liver cancer-related genes that were dysregulated following neonatal exposure to BDE-99. Our findings provide novel insights that early life exposure to POPs can have a life-long impact on disease risk, which may partly be regulated by the gut microbiome.

View article Supplementary data

EXPOSURE SCIENCES

FEATURED

Children with Amalgam Dental Restorations Have Significantly Elevated Blood and Urine Mercury Levels FREE

Lei Yin, Simon Lin, Anne O Summers, Van Roper, Matthew J Campen ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 104–126,
https://doi.org/10.1093/toxsci/kfab108

Abstract ▲

Human exposure to organic mercury (Hg) as methylmercury (MeHg) from seafood consumption is widely considered a health risk because pure methylmercury is extremely neurotoxic. In contrast, the clinical significance of Hg exposure from amalgam (AMG) dental restorations, the only other major nonoccupational source of Hg exposure, has long been debated. Here, we examined data from the two most recent National Health and Nutrition Examination Surveys (NHANES) on 14 181 subjects to assess the contributions of seafood consumption versus AMG to blood total mercury (THg), inorganic mercury (IHg), and methyl mercury (MeHg) and to urine creatinine corrected mercury (UTHg). All subjects were also classified as to their self-reported qualitative consumption of seafood (59% fish and 44% shellfish). Subjects with restorations were grouped into three groups (0) those without AMG (64.4%), (1) those with 1–5 dental AMG restorations (19.7%), (2) those with more than five AMG (16%). Seafood consumption increased total mercury in urine (UTHg) and total mercury (THg) and methyl mercury (MeHg) in blood, but unlike AMG, seafood did not increase blood inorganic mercury (IHg). Using stratified covariate (ANOVA) and multivariate (GLM) analyses revealed a strong correlation of blood (THg and IHg) and urine (UTHg) levels with the number of AMGs. In a subpopulation without fish consumption, having more than five AMG restorations raised blood THg (103%), IHg (221%), and urine UTHg (221%) over the group without AMG. The most striking difference was noted in classification by age: subjects under 6 years old with more than five AMG restorations had the highest blood IHg and

urine UTHg among all age groups. Elevation of bivalent IHg on a large scale in children warrants urgent in-depth risk assessment with specific attention to genetic- and gender-associated vulnerabilities.

View article

ORGAN SPECIFIC TOXICOLOGY

Mast Cells Promote Nitrogen Mustard-Mediated Toxicity in the Lung Associated With Proinflammatory Cytokine and Bioactive Lipid Mediator Production

Angela Cruz-Hernandez, Ryan P Mendoza, Kathleen Nguyen, Anna Harder, Christopher M Evans ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 127–141, https://doi.org/10.1093/toxsci/kfab107

Abstract ▲

Sulfur mustard (SM) has been widely used as a chemical warfare agent including most recently in Syria. Mice exposed to SM exhibit an increase in pro-inflammatory cytokines followed by immune cell infiltration in the lung, however, the mechanisms leading to these inflammatory responses has not been completely elucidated. Mast cells are one of the first responding innate immune cells found at the mucosal surfaces of the lung and have been reported to be activated by SM in the skin. Therefore, we hypothesized that nitrogen mustard (NM: a surrogate for SM) exposure promotes activation of mast cells causing chronic respiratory inflammation. To assess the role of mast cells in NM-mediated pulmonary toxicity, we compared the effects of NM exposure between C57BL/6 and B6.Cg-KitW-sh/HNihrJaeBsmJ ($Kit^{W\text{-}sh}$; mast cell deficient) mice. Lung injury was observed in C57BL/6J mice following NM exposure (0.125 mg/kg) at 72 h, which was significantly abrogated in $Kit^{W\text{-}sh}$ mice. Although both strains exhibited damage from NM, C57BL/6J mice had higher inflammatory cell infiltration and more elevated prostaglandin D_2 (PGD_2) present in bronchoalveolar lavage fluid compared with $Kit^{W\text{-}sh}$ mice. Additionally, we

utilized murine bone marrow-derived mast cells to assess NM-induced early and late activation. Although NM exposure did not result in mast cell degranulation, we observed an upregulation in PGD_2 and IL-6 levels following exposure to NM. Results suggest that mast cells play a prominent role in lung injury induced by NM and may contribute to the acute and potentially long-term lung injury observed caused by SM.

View article Supplementary data

The Impact of Di-Isononyl Phthalate Exposure on Specialized Epithelial Cells in the Colon

Karen Chiu, Shah Tauseef Bashir, Justin Chiu, Romana A Nowak, Jodi A Flaws

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 142–153, https://doi.org/10.1093/toxsci/kfab105

Abstract ▲

Di-isononyl phthalate (DiNP) is a high-molecular-weight phthalate commonly used as a plasticizer for polyvinyl chloride and other end products, such as medical devices and construction materials. Most of our initial exposure to DiNP occurs by ingestion of DiNP-contaminated foods. However, little is known about the effects of DiNP on the colon. Therefore, the goal of this study was to test the hypothesis that DiNP exposure alters immune responses and impacts specialized epithelial cells in the colon. To test this hypothesis, adult female mice were orally dosed with corn-oil vehicle control or doses of DiNP ranging from 20 µg/kg/d to 200 mg/kg/d for 10–14 days. After the dosing period, mice were euthanized in diestrus, and colon tissues and sera were collected for histological, genomic, and proteomic analysis of various immune factors and specialized epithelial cells. Subacute exposure to DiNP significantly increased protein levels of Ki67 and MUC2, expression of a Paneth cell marker (*Lyz1*), and estradiol levels in sera compared with control. Gene expression of mucins (*Muc1*, *Muc2*, *Muc3a*, and *Muc4*), Toll-like receptors (*Tlr4* and *Tlr5*), and specialized epithelial cells (*ChgA*, *Lgr5*, *Cd24a*, and *Vil1*) were not significantly

different between treatment groups and control. Cytokine levels of IL-1RA and CXCL12 were also not significantly different between DiNP treatment groups and control. These data reveal that DiNP exposure increases circulating estradiol levels and gene expression in specialized epithelial cells with immune response capabilities (eg, goblet and Paneth cells) in the mouse colon, which may initiate immune responses to prevent further damage in the colon.

View article Supplementary data

REGULATORY SCIENCE, RISK ASSESSMENT, AND DECISION MAKING

Potency Ranking of Per- and Polyfluoroalkyl Substances Using High-Throughput Transcriptomic Analysis of Human Liver Spheroids FREE

Anthony J F Reardon, Andrea Rowan-Carroll, Stephen S Ferguson, Karen Leingartner, Remi Gagne ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 154–169, https://doi.org/10.1093/toxsci/kfab102

Abstract ▲

Per- and polyfluoroalkyl substances (PFAS) are some of the most prominent organic contaminants in human blood. Although the toxicological implications of human exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are well established, data on lesser-understood PFAS are limited. New approach methodologies (NAMs) that apply bioinformatic tools to high-throughput data are being increasingly considered to inform risk assessment for data-poor chemicals. The aim of this study was to compare the potencies (ie, benchmark concentrations: BMCs) of PFAS in primary human liver microtissues (3D spheroids) using high-throughput transcriptional profiling. Gene expression changes were measured using TempO-seq, a templated, multiplexed RNA-sequencing platform. Spheroids were exposed for 1 or 10 days to increasing concentrations of 23 PFAS in 3 subgroups: carboxylates (PFCAs), sulfonates

(PFSAs), and fluorotelomers and sulfonamides. PFCAs and PFSAs exhibited trends toward increased transcriptional potency with carbon chain-length. Specifically, longer-chain compounds (7–10 carbons) were more likely to induce changes in gene expression and have lower transcriptional BMCs. The combined high-throughput transcriptomic and bioinformatic analyses support the capability of NAMs to efficiently assess the effects of PFAS in liver microtissues. The data enable potency ranking of PFAS for human liver cell spheroid cytotoxicity and transcriptional changes, and assessment of *in vitro* transcriptomic points of departure. These data improve our understanding of the possible health effects of PFAS and will be used to inform read-across for human health risk assessment.

View article Supplementary data

Reliability of the AR-CALUX® *In Vitro* Method Used to Detect Chemicals with (Anti)Androgen Activity: Results of an International Ring Trial

Anne Milcamps, Roman Liska, Ingrid Langezaal, Warren Casey, Matthew Dent ...

Toxicological Sciences, Volume 184, Issue 1, November 2021, Pages 170–182, https://doi.org/10.1093/toxsci/kfab078

Abstract ▲

The AR-CALUX® *in vitro* method is a reporter gene-based transactivation method where endocrine active chemicals with androgenic or anti-androgenic potential can be detected. Its primary purpose is for screening chemicals for further prioritization and providing mechanistic (endocrine mode of action) information, as defined by the Organisation of Economic Cooperation and Development (OECD) conceptual framework for the testing and assessment of endocrine-disrupting chemicals. This article describes the conduct and results of an international ring trial with 3 EU-NETVAL laboratories and the test method developer. It was organized by EURL ECVAM to validate the method by testing 46 chemicals. A very good reproducibility within and between laboratories

was concluded (94.7–100% and 100% concordance of classification) with low within and between laboratory variability (less than 2.5% CV on EC_{50} values). Moreover, the variability is within the range of other validated, mechanistically similar methods. In comparison to the AR-reference list compiled by ICCVAM, an almost 100% concordance of classifications was obtained. This method allows the detection of the agonist and antagonist properties of a chemical. A specificity control test was developed during the validation study and added to the antagonist assay rendering the assay more specific. A comparison is made with the mechanistically similar methods AR-EcoScreen™ and 22Rv1/MMTV GR-KO TA. The AR-CALUX® method was approved for inclusion in the recently updated OECD test guideline TG458 which incorporates all 3 methods.

View article Supplementary data

Front Matter Table of Contents

All issues

About Toxicological Sciences
Editorial Board
Policies
Author Guidelines
Facebook
Twitter
Purchase
Recommend to your Library
Advertising and Corporate Services
Journals Career Network

Toxicological Sciences

Online ISSN 1096-0929
Print ISSN 1096-6080

About Us
Connect