DESCRIPTION

*Toxicology and Applied Pharmacology* publishes original scientific research of relevance to animals or humans pertaining to the action of chemicals, drugs, or chemically-defined natural products.

Regular articles address mechanistic approaches to physiological, pharmacologic, biochemical, cellular, or molecular understanding of toxicologic/pathologic lesions and to methods used to describe these responses. Safety Science articles address outstanding state-of-the-art preclinical and human translational characterization of drug and chemical safety employing cutting-edge science. Highly significant Regulatory Safety Science articles will also be considered in this category. Papers concerned with alternatives to the use of experimental animals are encouraged.

Short articles report on high impact studies of broad interest to readers of *TAAP* that would benefit from rapid publication. These articles should contain no more than a combined total of four figures and tables. Authors should include in their cover letter the justification for consideration of their manuscript as a short article.

*TAAP* also issues a standing call for outstanding Invited Review Articles. Potential authors should contact the Editor-In-Chief and complete an Invited Review Proposal Form before preparing or submitting their Review Article.

**Benefits to authors**

We also provide many author benefits, such as free PDFs, a liberal copyright policy, special discounts on Elsevier publications and much more. Please click here for more information on our author services.

Please see our Guide for Authors for information on article submission. If you require any further information or help, please visit our Support Center.

AUDIENCE

Toxicologists, pharmacologists, cancer researchers, epidemiologists, molecular and cell biologists

IMPACT FACTOR

2019: 3.347 © Clarivate Analytics Journal Citation Reports 2020
ABSTRACTING AND INDEXING

Scopus
PubMed/Medline
EM Biology
BIOSIS Citation Index
Chemical Abstracts
Chemical Hazards Index
Current Contents - Life Sciences and Clinical Medicine
Embase
International Pharmaceutical Abstracts
Medical Abstracts Newsletter
Research Alert
Safety Science Abstracts
Science Citation Index
Toxicology Abstracts

EDITORIAL BOARD

Editor-in-Chief
Lawrence H. Lash, Wayne State University Department of Pharmacology, Detroit, Michigan, United States

Associate Editors
Nihal Ahmad, University of Wisconsin-Madison Department of Dermatology, Madison, Wisconsin, United States
Yasunobu Aoki, National Institute for Environmental Studies, Ibaraki, Japan
Barbara D. Beck, Gradco LLC, Cambridge, Massachusetts, United States
Aaron B. Bowman, Purdue University School of Health Sciences, West Lafayette, Indiana, United States
Joseph P. Bressler, Kennedy Krieger Institute, Baltimore, Maryland, United States
Yongxiu Cao, Xi'an Jiaotong University Department of Pharmacology, Xi'an, China
Fei Chen, Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, Michigan, United States
Sek-Chuen Chow, Monash University - Malaysia Campus, Bandar Sunway, Malaysia
Daniel J. Conklin, University of Louisville School of Medicine Division of Environmental Medicine, Louisville, Kentucky, United States
George B. Corcoran, Wayne State University Department of Pharmaceutical Sciences, Detroit, Michigan, United States
Deborah A. Cory-Slechta, University of Rochester Medical Center Department of Environmental Medicine, Rochester, New York, United States
Max Costa, New York University Department of Environmental Medicine, New York, United States
Jamie DeWitt, East Carolina University Brody School of Medicine, Greenville, North Carolina, United States
Rakesh Dixit, AstraZeneca Medimmune, Gaithersburg, MD, United States
Bruce Fowler, ICF International Inc, Fairfax, Virginia, United States
Seishiro Hirano, National Institute for Environmental Studies Center for Health and Environmental Risk Research, Tsukuba-Shi, Ibaraki-Ken, Japan
Sam Kacew, University of Ottawa R Samuel McLaughlin Centre for Population Health Risk Assessment, Ottawa, Ontario, Canada
Georges E.N. Kass, European Food Safety Authority, Parma, Italy
Aileen Keating, Iowa State University Department of Animal Science, Ames, Iowa, United States
William Kelce, Voisin Consulting Life Sciences Cambridge, Cambridge, Massachusetts, United States
M. Firoze Khan, The University of Texas Medical Branch at Galveston Department of Pathology, Galveston, Texas, United States
Debra L. Laskin, Rutgers University Ernest Mario School of Pharmacy, Piscataway, New Jersey, United States
Jerold A. Last, University of California Davis Department of Internal Medicine, Sacramento, California, United States
David A. Lawrence, Wadsworth Center, Albany, New York, United States
Ke Jian (Jim) Liu, University of New Mexico College of Pharmacy, Albuquerque, New Mexico, United States
Jonathan Maher, Genentech Inc, South San Francisco, California, United States
Bhagavatula Moorthy, Baylor College of Medicine Department of Pediatrics - Infectious Diseases, Houston, Texas, United States
Hasan Mukhtar, University of Wisconsin-Madison Department of Dermatology, Madison, Wisconsin, United States
Carlos Palmeira, University of Coimbra Center for Neuroscience and Cell Biology, Coimbra, Portugal
Jingbo Pi, China Medical University School of Public Health, Shenyang, China
Anabela Pinto Rolo, University of Coimbra Faculty of Sciences and Technology, Coimbra, Portugal
Carey Nat Pope, Oklahoma State University Center for Veterinary Sciences, Stillwater, Oklahoma, United States
Stephen B. Pruett, Mississippi State University Department of Basic Sciences, University, Mississippi, United States
Zhifeng Qi, Xuanwu Hospital, Beijing, China
Irfan Rahman, University of Rochester Medical Center Department of Neuroscience and Pharmacology, Rochester, New York, United States
Aramandla Ramesh, Meharry Medical College Department of Environmental Toxicology, Nashville, Tennessee, United States
Robert H. Rice, University of California Davis Department of Environmental Toxicology, Davis, California, United States
Jason R. Richardson, Northeastern Ohio University Department of Pharmaceutical Science, Rootstown, Ohio, United States
Jim Riviere, Kansas State University College of Veterinary Medicine, Manhattan, Kansas, United States
Allen J. Rosenspire, Wayne State University School of Medicine Department of Biochemistry Microbiology & Immunology, Detroit, Michigan, United States
Ivan Rusyn, Texas A&M University Department of Veterinary Integrative Biosciences, College Station, Texas, United States
Konstantin Salnikow, National Cancer Institute Cell and Cancer Biology Branch, Bethesda, Maryland, United States
Masao Sato, Tokushima Bunri University Faculty of Pharmaceutical Sciences, Tokushima, Japan
Timothy J. Shafer, Environmental Protection Agency Division of Integrated Systems Toxicology, Research Triangle Park, North Carolina, United States
Jiangang Shen, University of Hong Kong Li Ka Shing Faculty of Medicine, Pokfulam, Hong Kong, Hong Kong
Angela Slitt, University of Rhode Island Department of Biomedical and Pharmaceutical Sciences, Kingston, Rhode Island, United States
Miguel Sogorb, Miguel Hernandez University of Elche Institute of Bioengineering, Elche, Spain
J. Christopher States, University of Louisville Department of Pharmacology and Toxicology, Louisville, Kentucky, United States
Lesster G. Sultatos, New Jersey Medical School Department of Pharmacology and Physiology, Newark, New Jersey, United States
Todd A. Thompson, University of New Mexico Department of Pharmaceutical Sciences, Albuquerque, New Mexico, United States
Richard R. Vaillancourt, The University of Arizona Department of Pharmacology and Toxicology, Tucson, Arizona, United States
Henk Van Loveren, Maastricht University, Maastricht, Netherlands
Libia Vega Loyo, Center for Research and Advanced Studies of the National Polytechnic Institute Department of Toxicology, Mexico City, Mexico
Lewis Josh Watson, University of Pikeville Kentucky College of Osteopathic Medicine, Pikeville, Kentucky, United States
Elizabeth V. Wattenberg, University of Minnesota Division of Environmental Health Sciences, Minneapolis, Minnesota, United States
James Willard, Center for Drug Evaluation and Research Division of Cardiovascular and Renal Products, Silver Spring, Maryland, United States
Calvin C. Willhite, Risk Sciences International, Ottawa, Ontario, Canada
Bin Xiang, The Second Hospital of Dalian Medical University, Dalian, China
Timothy R. Zacharewski, Michigan State University Department of Biochemistry and Molecular Biology, East Lansing, Michigan, United States
Helmut Zarbl, Rutgers Robert Wood Johnson Medical School Department of Environmental and Occupational Medicine, Piscataway, New Jersey, United States
Qiang Zhang, Emory University School of Public Health, Atlanta, Georgia, United States
Xin-Yu Zhang, Shanghai Jiao Tong University School of Public Health, Shanghai, China
Yuxin Zheng, Qingdao University School of Public Health, Qingdao, China

Editors Emeriti
Edward Bresnick
Scott W. Burchiel
A. Wallace Hayes
Robert A. Neal
Gabriel L. Plaa
C. Boyd Shaffer
I. Glenn Sipes
Michael P. Waalkes

Founding Editors
Frederick Coulston
Harry W. Hays
Arnold J. Lehman
GUIDE FOR AUTHORS

Your Paper Your Way
We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.
To find out more, please visit the Preparation section below.

INTRODUCTION
Toxicology and Applied Pharmacology publishes original scientific research of relevance to animals or humans pertaining to the action of chemicals, drugs, or chemically-defined natural products. Although many drugs are derived from plants, we generally do not consider manuscripts that study the biological effects of undefined plant extracts. In addition, studies that are replicative of science on substances that have already been well reported (e.g., amelioration of oxidative stress) are discouraged.

Regular articles address mechanistic approaches to physiological, pharmacologic, biochemical, cellular, or molecular understanding of toxicologic/pathologic lesions and to methods used to describe these responses. Safety Science articles address outstanding state-of-the-art preclinical and human translational characterization of drug and chemical safety employing cutting-edge science. Highly significant Regulatory Safety Science articles will also be considered in this category. Papers concerned with alternatives to the use of experimental animals are encouraged.

Short articles report on high impact studies of broad interest to readers of TAAP that would benefit from rapid publication. These articles should contain no more than a combined total of four figures and tables. Authors should include in their cover letter the justification for consideration of their manuscript as a short article.

TAAP also issues a standing call for outstanding Invited Review Articles. Potential authors should contact the Editor-In-Chief and complete an Invited Review Proposal Form before preparing or submitting their Review Article. Invited reviews are intended to be from researchers with documented expertise who have contributed significantly to an area of science relevant to toxicology and/or pharmacology.

Types of Papers
The following types of articles will be considered for publication: Research Paper, Safety Science Articles, Short High Impact Articles, and Invited Reviews.

Research Paper address mechanistic approaches to physiological, pharmacologic, biochemical, cellular, or molecular understanding of toxicologic/pathologic lesions and to methods used to describe these responses. Regular Articles should be approximately 25 to 35 pages with double line spacing including references but not including figures. Safety Science articles address outstanding state-of-the-art preclinical and human translational characterization of drug and chemical safety employing cutting-edge science. Highly significant Regulatory Safety Science articles will also be considered in this category. Papers concerned with alternatives to the use of experimental animals are encouraged.

Short articles (Short Communications) report on high impact studies of broad interest to readers of Toxicology and Applied Pharmacology that would benefit from rapid publication. These articles should contain no more than a combined total of four figures and tables and should be approximately 12 to 15 pages with double line spacing including references. Authors should include in their cover letter the justification for consideration of their manuscript as a short article and mention that this belongs to the article type Short articles report on high impact.

Invited Review - Toxicology and Applied Pharmacology also issues a standing call for outstanding Invited Review Articles. Potential authors should contact the Editorial Office (tox@elsevier.com) and complete an Invited Review Proposal Form before preparing or submitting their Review. These reviews are expected to on timely topics relevant to toxicology and/or pharmacology from researchers with documented expertise in those topics.
Letter to the Editors refer to an article published in the journal and includes omissions or reflects differences in opinion, based on scientific evidence. These Letters to the Editors should not exceed 1000 words and 5 references. If needed one table or figure can be added. Authors of the involved article will always be asked by the Editors for a rebuttal that will linked online to the Letter to the Editor. These rebuttals should also contain no more than 1000 words, 5 references and if needed one table or figure. In principle, a single round of Letters to the Editors exchange will be considered in order to contain the discussion on a given topic.

Submission checklist
You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
- E-mail address
- Full postal address

All necessary files have been uploaded:
Manuscript:
- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print
Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

Further considerations
- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- A competing interests statement is provided, even if the authors have no competing interests to declare
- Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

BEFORE YOU BEGIN
Diethyl ether is considered unacceptable as an agent for either anesthesia or euthanasia according to the American Veterinary Medical Association (AVMA Guidelines for the Euthanasia of Animals: 2013 Edition). Accordingly, studies that report use of diethyl ether or its derivatives in animal studies will not be considered for publication. Other agents, including chloral hydrate and chloroform, are also considered by the AVMA as inappropriate for use in animal studies. Any manuscript reporting use of these agents for anesthesia or euthanasia will not be considered for publication.

Ethics in publishing
Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

Use of Animals in Experimental Studies
1. All studies involving the use of animals must contain language and, if necessary, support documentation indicating that the studies were conducted in accordance with the laws and regulations of governing authorities. A clear statement regarding approval by the local Institutional Animal Care and Use Committee (IACUC) or equivalent must be made in the Methods Section.
2. It is the policy of TAAP that no pictures of dead or moribund animals will be published in the journal.
3. Use of agents for anesthesia and/or euthanasia must be specified in the manuscript.

Use of humans, human tissues, and clinical trials
1. All studies involving humans or human tissues must be approved by the appropriate Institutional Review Boards (IRB) in accordance with laws and policies of governing authorities. A clear statement regarding the use of humans in studies and the source of human tissues must be made in the Methods Section with appropriate references to Informed Consent and Research Protections, if required by the IRB. Support documentation may also be request by the journal or its editorial board.

**Studies in humans and animals**

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

**Declaration of interest**

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors should complete the declaration of interest statement using this template and upload to the submission system at the Attach/Upload Files step. **Note: Please do not convert the .docx template to another file type. Author signatures are not required.** If there are no interests to declare, please choose: 'Declarations of interest: none' in the template. This statement will be published within the article if accepted. More information.

**Submission declaration and verification**

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. To verify originality, your article may be checked by the originality detection service Crossref Similarity Check.

**Preprints**

Please note that preprints can be shared anywhere at any time, in line with Elsevier's sharing policy. Sharing your preprints e.g. on a preprint server will not count as prior publication (see 'Multiple, redundant or concurrent publication' for more information).

**Use of inclusive language**

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.
Author contributions
For transparency, we encourage authors to submit an author statement file outlining their individual contributions to the paper using the relevant CRediT roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Authorship statements should be formatted with the names of authors first and CRediT role(s) following. More details and an example

Changes to Authorship
This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts:
Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Editor-In-Chief of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been resolved to the satisfaction of the Editor-In-Chief.
After the accepted manuscript is published: TAAP will not accept any requests to add, delete, or rearrange author names in an article.

Article transfer service
This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal. More information.

Copyright
Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

For gold open access articles: Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (more information). Permitted third party reuse of gold open access articles is determined by the author's choice of user license.

Author rights
As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing
Find out how you can share your research published in Elsevier journals.

Role of the funding source
You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated.
Open access
Please visit our Open Access page for more information.

Elsevier Researcher Academy
Researcher Academy is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Language (usage and editing services)
Please write your text in good English (American or British usage is accepted, but not a mixture of these). Articles that in the opinion of Editor-In-Chief, Associate Editors and/or Reviewers do not meet a high English language standard will be rejected on this technical basis. Manuscripts rejected for language issues may be reconsidered and resubmitted after the author has demonstrated in a cover letter that the manuscript has now met the English language standard. Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop (http://webshop.elsevier.com/languageediting/) or visit our customer support site (https://service.elsevier.com) for more information.

Submission
Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Should you be unable to provide an electronic version, please contact the editorial office prior to submission at e-mail: tox@elsevier.com; telephone: +1 (619) 699-6275; or fax: +1 (619) 699-6211.

Experimental procedures
All animal experiments should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, the European Communities Council Directive of 24 November 1986 (86/609/EEC) or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. All animal studies need to ensure they comply with the ARRIVE guidelines. More information can be found at http://www.nc3rs.org.uk/page.asp?id=1357.

PREPARATION
NEW SUBMISSIONS
Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process. Authors are requested to carefully proofread the PDF file generated by the system before finalizing submission to ensure that all text is formatted properly and that all figures are clear and readable.

As part of the Your Paper Your Way service, you may choose to submit your manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or layout that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately.

References
There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.
**Formatting requirements**

There are no strict formatting requirements with the exceptions noted below. All manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions. If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

Please ensure the text of your paper is double-spaced and has consecutive line numbering—this is an essential peer review requirement.

**Figures and tables embedded in text**

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

**Peer review**

This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor’s decision is final. More information on types of peer review.

**REVISED SUBMISSIONS**

**Use of word processing software**

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

**Article structure**

**Preparation of Manuscript.**

Manuscripts text should have double line spacing and references should be single-spaced. Pages should be numbered consecutively and organized as follows:

The title Page (p. 1) should contain the article title, authors’ names and complete affiliations, footnotes to the title, and the address for manuscript correspondence (including e-mail address and telephone and fax numbers). The article title should be comprehensive and descriptive: proprietary names must not be used in titles, but may be identified in footnotes.

Page 2 should contain an abstract. The abstract should be limited to 250 words but must contain a concise summary of what was done, the results obtained, and valid conclusions which are drawn therefrom. It must mention the compounds or families of compounds studied, their actions, and the species of animals. It must contain important words which are used as index terms, but not proprietary names. Keywords should be listed immediately after the abstract.

Format. The following text sections should be used. Introduction. State why the investigation was carried out, note any relevant published work, and delineate the objective of the investigation.

Methods. New methods or significant improvements of methods or changes in old methods must be described. Methods for which adequate reference can be cited are not to be described. In the Methods section, authors should draw attention to any particular chemical or biological hazards that may be involved in carrying out the experiments described. Any relevant safety precautions should be described: if an accepted code of practice has been followed, a reference to the relevant standards should be given. Details regarding animal housing conditions and all animal procedures should be given.
Results. Duplication between the text of this section and material presented in tables and figures should be avoided. Tabular presentation of masses of negative data must be avoided and replaced with a statement in the text whenever possible. The statement must include (a) what was done, (b) how it was done, (c) how the data were analyzed, (d) a measure of variability, and (e) the significance of the result.

Discussion. This section must relate to the significance of the work to existing knowledge in the field and indicate the importance of the contribution of this study. Needless detailed recapitulation of the results must be avoided. Unsupported hypotheses and speculation should be omitted.

Subdivision - unnumbered sections
Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Authors should draw attention to any particular chemical or biological hazards that may be involved in carrying out the experiments described. Any relevant safety precautions should be described: if an accepted code of practice has been followed, a reference to the relevant standards should be given. Details regarding animal housing should also be noted.

Results
Results should be clear and concise.

Duplication between the text of this section and material presented in tables and figures should be avoided and replaced with a statement in the text whenever possible. The statement must include (a) what was done, (b) how it was done, (c) how the data were analyzed, (d) a measure of variability, and (e) the significance of the result.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is sometimes appropriate. Avoid extensive citations and discussion of published literature.

Needless detailed recapitulation of the results must be avoided. Unsupported hypotheses and speculation should also be omitted.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information
• **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• **Author names and affiliations.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lowercase superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
• **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

**Highlights**
Highlights are mandatory for this journal as they help increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

**Abstract**
A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

The abstract should be limited to 250 words. It must mention the compounds or families of compounds studied, their actions, and the species of animals, but must not contain proprietary names.

**Graphical abstract**
Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site. Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

**Keywords**
Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

**Abbreviations**
Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

**Acknowledgements**
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

**Formatting of funding sources**
List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.
If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units will be in general accordance with the International System (SI) as adopted by the 11th General Conference on Weights and Measures. Common abbreviations to be used in this journal are:

- m meter
- ppm parts per million
- cm centimeter
- cpm counts per minute
- mm millimeter
- dpm disintegrations per minute
- um micrometer
- sc subcutaneous
- nm nanometer
- ic intracutaneous
- kg kilogram
- im intramuscular
- g gram
- ip intraperitoneal
- mg milligram iv intravenous
- ug microgram
- po oral
- ng nanogram
- LD50 medial lethal dose
- ml milliliter
- LC50 medial lethal concentration
- >ul microliter
- Hz hertz mol mole
- s seconds
- M molar
- min minutes
- mM millimolar
- h hours
- uM micromolar
- SD standard deviation
- N normal
- SE standard error
- Ci Curie TLV threshold limit value
- X mean

Math formulae
Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Proprietary names of substances and names and addresses of suppliers should be identified in footnotes. If the paper has been presented orally in whole or part, the date, and occasion should be included in a footnote.

Footnotes
Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

Artwork
Image manipulation
Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

Electronic artwork
General points
- Make sure you use uniform lettering and sizing of your original artwork.
- Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Indicate per figure if it is a single, 1.5 or 2-column fitting image.
- For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
- Please note that individual figure files larger than 10 MB must be provided in separate source files.

A detailed guide on electronic artwork is available.
You are urged to visit this site; some excerpts from the detailed information are given here.
Formats
Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):
EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.
TIFF (or JPEG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi.
TIFF (or JPEG): Bitmapped line drawings: use a minimum of 1000 dpi.
TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.
Please do not:
- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.
- Supply files that are too low in resolution.
- Submit graphics that are disproportionately large for the content.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Figure captions
Ensure that each illustration has a caption. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables
Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References
Unpublished results or personal communications should be cited as such in the text.
Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either ‘Unpublished results’ or ‘Personal communication’. Citation of a reference as ‘in press’ implies that the item has been accepted for publication and a copy of the title page of the relevant article must be submitted.

Reference links
Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software
Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley. Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal’s style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes from different reference management software.

Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/toxicology-and-applied-pharmacology
When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice.

Reference formatting
There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by
the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

**Reference style**

**Text:** All citations in the text should refer to:
1. **Single author:** the author's name (without initials, unless there is ambiguity) and the year of publication;
2. **Two authors:** both authors' names and the year of publication;
3. **Three or more authors:** first author's name followed by 'et al.' and the year of publication.

Citations may be made directly (or parenthetically). Groups of references can be listed either first alphabetically, then chronologically, or vice versa.

**Examples:**
- 'as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999).... Or, as demonstrated (Jones, 1999; Allan, 2000)... Kramer et al. (2010) have recently shown ...'

**List:** References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.

**Examples:**
- Reference to a journal publication:
- Reference to a journal publication with an article number:
- Reference to a book:
- Reference to a chapter in an edited book:
- Reference to a website:
- Reference to a dataset:

**Journal abbreviations source**

Journal names should be abbreviated according to the List of Title Word Abbreviations.

**Video**

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

**Supplementary material**

Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to
supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

**Research data**

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the research data page.

**Data linking**

If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the database linking page.

For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

**Mendeley Data**

This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. Before submitting your article, you can deposit the relevant datasets to Mendeley Data. Please include the DOI of the deposited dataset(s) in your main manuscript file. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the Mendeley Data for journals page.

**Data in Brief**

You have the option of converting any or all parts of your supplementary or additional raw data into one or multiple data articles, a new kind of article that houses and describes your data. Data articles ensure that your data is actively reviewed, curated, formatted, indexed, given a DOI and publicly available to all upon publication. You are encouraged to submit your article for Data in Brief as an additional item directly alongside the revised version of your manuscript. If your research article is accepted, your data article will automatically be transferred over to Data in Brief where it will be editorially reviewed and published in the open access data journal, Data in Brief. Please note an open access fee of 600 USD is payable for publication in Data in Brief. Full details can be found on the Data in Brief website. Please use this template to write your Data in Brief.

**MethodsX**

You have the option of converting relevant protocols and methods into one or multiple MethodsX articles, a new kind of article that describes the details of customized research methods. Many researchers spend a significant amount of time on developing methods to fit their specific needs or setting, but often without getting credit for this part of their work. MethodsX, an open access journal, now publishes this information in order to make it searchable, peer reviewed, citable and reproducible. Authors are encouraged to submit their MethodsX article as an additional item directly alongside the revised version of their manuscript. If your research article is accepted, your methods article will
automatically be transferred over to MethodsX where it will be editorially reviewed. Please note an open access fee is payable for publication in MethodsX. Full details can be found on the MethodsX website. Please use this template to prepare your MethodsX article.

Data statement
To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the Data Statement page.

AFTER ACCEPTANCE

Online proof correction
To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors. If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.
We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Offprints
The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Author Services. Corresponding authors who have published their article gold open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES
Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch. You can also check the status of your submitted article or find out when your accepted article will be published.

© Copyright 2018 Elsevier | https://www.elsevier.com