

GDCh-Advisory Committee
on Existing Chemicals (BUA)

**Evaluation of OECD Screening Tests
421 (Reproduction/Developmental Toxicity
Screening Test) and 422 (Combined Repeated
Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test)**

BUA Report 229
(February 2001)



S. Hirzel

Wissenschaftliche Verlagsgesellschaft 2002

GDCh-Advisory Committee on Existing Chemicals (BUA, February 2001)

Chairman:

Prof. Dr. H. GREIM, Technische Universität München, Weihenstephan

Members:

Prof. Dr. H. DREXLER, Institut für Arbeits-, Sozial- und Umweltmedizin, Universität Erlangen

Prof. Dr. Dr. H. GELBKE, BASF AG, Toxikologie, Ludwigshafen am Rhein

Frau Prof. Dr. U. GUNDERT-REMY, Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, Berlin

Dr. H. von HOLLEBEN, Verband der Chemischen Industrie, Frankfurt am Main

Prof. Dr. H. HULPKE, Bayer AG, Konzernstab KS-QUS, Leverkusen

Priv.-Doz. Dr. Dr. A. KAPPOS, Behörde für Arbeit, Gesundheit und Soziales der Freien Hansestadt Hamburg

Dr. J. KUTSCHER, Berufsgenossenschaft der Chemischen Industrie, Heidelberg

Dr. C. MEICHSNER, Infraserv GmbH & Co. Höchst KG, Umwelt/Sicherheit, Frankfurt am Main

Prof. Dr. R. NAGEL, Institut für Hydrobiologie der Technischen Universität Dresden

Dir. und Prof. Dr. H. NEIDHARD, Umweltbundesamt, Berlin (up to October 2000)

Dr. N. RUPPRICH, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund

Prof. Dr. R. ZELLNER, Institut für Physikalische und Theoretische Chemie der Universität Essen (Vice Chairman)

Collaborators and Guests:

Frau Dr. H. GREIM, Technische Universität München, Weihenstephan

Frau Dr. B. HEINRICH-HIRSCH, Fachgebiet 825 des Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, Berlin

Dr. J. HELLWIG, BASF AG, Toxikologie, Ludwigshafen

Frau Dr. B. HOLZUM, Bayer AG, Toxikologie, Wuppertal

Frau Dr. U. REUTER, Technische Universität München, Weihenstephan

Dr. F. WELSCH, Orbitox, North Carolina, USA

Frau Dr. K. WIDMANN, Technische Universität München, Weihenstephan

Responsible at the BMU:

MinR Prof. Dr. U. SCHLOTTMANN, Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, Bonn

GDCh-Office:

Dr. H. BEHRET, GDCh, Frankfurt am Main

**Evaluation of OECD Screening Tests 421
(Reproduction/Developmental Toxicity Screening
Test) and 422 (Combined Repeated Dose Toxicity
Study with the Reproduction/Developmental
Toxicity Screening Test)**

BUA Report 229
(February 2001)

edited by the GDCh-Advisory Committee
on Existing Chemicals

GDCh-Beratergremium
für Altstoffe (BUA)



S. Hirzel

Wissenschaftliche Verlagsgesellschaft 2002

Dr. H. Behret
Gesellschaft Deutscher Chemiker
Postfach 90 04 40
D-60444 Frankfurt am Main
E-Mail: boa@gdch.de
Homepage: <http://www.gdch.de>

Responsible at the BMU:
MinR Prof. Dr. U. Schlottmann
BMU
Postfach 12 06 29
D-53048 Bonn
E-Mail: schlottmann.ulrich@bmu.de

The work for this publication was sponsored by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit (BMU) / Federal Environmental Agency (Umweltbundesamt)) and the German Chemical Industry Association (Verband der Chemischen Industrie, VCI)

This book was carefully produced. Nevertheless, authors, editors and publisher do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

The use of general descriptive names, trade names, trademarks, etc. in a publication, even if not specifically identified, does not imply that these names are not protected by the relevant law and regulations.

Die Deutsche Bibliothek – CIP-Einheitsaufnahme

Evaluation of OECD screening tests 421 (reproduction, developmental toxicity screening test) and 422 (combined repeated dose toxicity study with the reproduction, developmental toxicity screening test) / ed. by the GDCh Advisory Committee on Existing Chemicals. [Transl. by P. Karbe] – (February 2001). – Stuttgart : Hirzel ; Stuttgart : Wiss. Verl.-Ges., 2002

(BUA Report ; 229)

Dt. Ausg. u. d. T.: Evaluierung der OECD Screening Tests 421 (Reproduction, developmental toxicity screening test) und 422 (Combined repeated dose toxicity study with the reproduction, developmental toxicity screening test)

ISBN 3-776-1200-6

All rights reserved. No part of this publication may be translated, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without permission in writing from the publisher.

© 2002 S. Hirzel Verlag, Birkenwaldstraße 44, 70191 Stuttgart

Printed on acid-free and low-chlorine paper.

Printing and binding: Druckpartner Rübelmann GmbH, Hemsbach
Printed in F.R. Germany

Preface

The Advisory Committee on Existing Chemicals of Environmental Relevance, BUA for short, was established in May 1982 to help the German federal government cope with the large task of dealing with existing chemicals. In an agreement between federal government, scientific community, and the chemical industry, it was associated with the German Chemical Society (GDCh-Gesellschaft Deutscher Chemiker) to ensure objective work, carried out in accordance with scientific principles.

At the end of 1997, the Committee was renamed 'GDCh Advisory Committee on Existing Chemicals' (abbreviation 'BUA' as before) and the statutes were revised to include EU level aspects of occupational safety for the handling of existing chemicals from then on.

The cooperation between authorities, industry, and the scientific community, upon which the BUA is based, has proven worthwhile. No other national or international body has dealt with the ecological and health-related effects of so many existing chemicals as the BUA. On the national level, the BUA has produced comprehensive reports on about 300 substances and carried out preliminary evaluation and classification (priority-setting) for approximately 200 more, as of 1997. Publication of the process leading to priority-setting, in addition to the BUA Reports, lends transparency to the Committee's work.

The BUA began an additional national project in 1997, which also selects and assesses existing chemicals with a lower production volume in the range of 100 - 1000 tonnes/ year. Comprehensive reports are published on chemicals suspected of having a hazardous potential. If the data available for substance assessment are insufficient, the gaps in knowledge are documented and, if necessary, investigations recommended.

The BUA, as expert committee, increasingly addresses broad scientific questions and problems, such as 'endocrine disruptors' and 'persistent organic pollutants' (POPs). Through such scientific projects the state of scientific knowledge is researched, documented, and published as 'BUA Reports'.

For a large number of existing chemicals there is very little or no information on reproductive toxicity. Therefore, the OECD developed the screening tests 421 (Reproduction/Developmental Toxicity Screening Test) and 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) which can be used in the initial evaluation of existing chemicals to provide limited information on possible effects on reproduction. The aim of the present report was to assess and evaluate these screening tests with respect to reproductive effects and decide to what extent they are to be recommended.

Munich, February 2001

Helmut Greim
BUA Chairman

Contents

Abbreviations	VIII
Summary	IX
1 Introduction	1
2 OECD Screening Test Guidelines 421 and 422 in Comparison to Existing Test Guidelines	5
2.1 Comparison with the One-Generation Study (OECD 415).....	5
2.2 Main differences compared to the oral 28-Day Study (OECD 402).....	23
2.3 Endpoint teratogenicity (partial comparison with OECD 414).....	24
3 Relevance of the OECD Screening Tests 421 and 422	25
3.1 Comparison of the results of screening tests and other studies on reproductive toxicity	25
3.2 Assessment of screening test results	28
3.3 Priority-setting for additional testing	32
4 Conclusions	34
5 References	36
Annex I: Substances for which OECD Screening Tests (421 or 422) and further tests for reproductive toxicity and repeated toxicity were performed	1 - 7
Annex II: Summary of the results of OECD Screening Tests 421 or 422	1 - 23

Abbreviations:

BUA	Advisory Committee on Existing Chemicals of the German Chemical Society
ECETOC	European Chemical Industry Ecotoxicology and Toxicology Centre
EPA	U.S. Environmental Protection Agency
EU	European Union
OECD	Organization for Economic Cooperation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances of the U.S. Environmental Protection Agency
JETOC	Japan Chemical Industry Ecology-Toxicology & Information Center
NOAEL	No Observed Adverse Effect Level
SIDS	Screening Information Data Sets

Evaluation of OECD Screening Tests 421 (Reproduction/Developmental Toxicity Screening Test) and 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test)

Summary

An expert panel of the Advisory Committee on Existing Chemicals (BUA) was assigned the task of evaluating OECD screening tests 421 (Reproduction/Developmental Toxicity Screening Test) and 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) with respect to toxic effects on reproduction. The initially planned “validation” of the above-mentioned OECD screening tests is not possible at the present time, as only 5 substances with proven reproductive toxicity have been investigated according to OECD screening test guidelines 421 or 422 and definitive guidelines or in further investigations, thus permitting a direct comparison of the test results. However, in each case, properties relevant to reproductive toxicity were also indicated by the screening tests.

For a comparison of OECD screening test guidelines 421 and 422 with definitive test guidelines, particularly OECD test guideline 415 (one-generation study), which has a similar study design, the main differences were compiled in a table and described in the text. Special reference was made to the very limited possibilities of detecting late post-natal and post-lactational manifestations, as well as to the relatively low statistical power of OECD screening tests 421 and 422. The aspect of teratogenicity was also shown to be incompletely covered.

To evaluate the relevance of the OECD screening tests, the results of 57 tests carried out according to OECD screening test guideline 421 or 422 were listed in a table and assessed and grouped according to the incidence of reproductive toxic effects to the parent animals or their offspring in relation to general toxic effects. Based on this grouping, a recommendation was made for deciding on the priority of carrying out further tests to determine and identify the hazard to reproduction of an existing substance.