Background Review Document
Reduced Murine Local Lymph Node Assay

Interagency Coordinating Committee on the Validation of Alternative Methods

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

2009

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

[This Page Intentionally Left Blank]

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Acronyms

ACD	Allergic contact dermatitis
ACE	Acetone
AOO	Acetone: olive oil (4:1 by volume)
BGIA	Berufsgenossenschaftliches Institut fur Arbeitsschutz (German Institute for Occupational Safety and Health)
BRD	Background review document
CASRN	Chemical Abstracts Service Registry Number
CESIO	Comite Europeen des Agents de Surface et de Leurs Intermediaires Organiques (European Committee of Surfactants and Their Organic Intermediates)
Conc.	Concentration tested
CPSC	U.S. Consumer Product Safety Commission
DBP	Dibutyl phosphate
DEP	Diethyl phthalate
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNCB	Dinitrochlorobenzene
EC3	Estimated concentration needed to produce a stimulation index of 3
ECPA	European Crop Protection Association
ECVAM	European Centre for the Validation of Alternative Methods
EFfCI	European Federation for Cosmetic Ingredients
EPA	U.S. Environmental Protection Agency
ESAC	European Centre for the Validation of Alternative Methods Scientific Advisory Committee
FDA	U.S. Food and Drug Administration
FR	*Federal Register*
GLP	Good Laboratory Practice
GPMT	Guinea Pig Maximization Test
HCA	Hexyl cinnamic aldehyde
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ILS	Integrated Laboratory Systems
ISO	International Organization for Standardization
IWG	Immunotoxicity Working Group
K_{ow}	Octanol-water partition coefficient
LLNA	Murine local lymph node assay

MEK	Methyl ethyl ketone
NA	Not applicable
NC	Not calculated
ND	No data
NICEATM	National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
PA	Pluronic acid
PG	Propylene glycol
RIFM	Research Institute for Fragrance Materials
rLLNA	Reduced murine local lymph node assay
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SI	Stimulation index
SOT	Society of Toxicology
TG	Test guideline
TNO	TNO Nutrition and Food Research Institute (Netherlands)
U.K.	United Kingdom
U.N.	United Nations
U.S.	United States
w/v	Weight-to-volume ratio

[This Page Intentionally Left Blank]

Interagency Coordinating Committee on the Validation of Alternative Methods: Agency Representatives

Agency for Toxic Substances and Disease Registry
• Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission
• Marilyn L. Wind, Ph.D. (Chair)
◊ Kristina Hatlelid, Ph.D.
Joanna Matheson, Ph.D.

Department of Agriculture
• Jodie Kulpa-Eddy, D.V.M. (Vice-Chair)
◊ Elizabeth Goldentyer, D.V.M.

Department of Defense
• Robert E. Foster, Ph.D.
◊ Patty Decot
Peter J. Schultheiss, D.V.M., D.A.C.L.A.M.
Harry Salem, Ph.D.

Department of Energy
• Michael Kuperberg, Ph.D.
◊ Marvin Stodolsky, Ph.D.

Department of the Interior
• Barnett A. Rattner, Ph.D.
◊ Sarah Gerould, Ph.D.

Department of Transportation
• George Cushmac, Ph.D.
◊ Steve Hwang, Ph.D.

Environmental Protection Agency
Office of Science Coordination and Policy
• Karen Hamernik, Ph.D.
Office of Research and Development
◊ Julian Preston, Ph.D.
Suzanne McMaster, Ph.D.
Office of Pesticide Programs
Amy Rispin, Ph.D.
Deborah McCall
OECD Test Guidelines Program
Jerry Smrchek, Ph.D.

• Principal agency representative
◊ Alternate principal agency representative

Food and Drug Administration
Office of Science
• Suzanne Fitzpatrick, Ph.D., D.A.B.T.
Center for Drug Evaluation and Research
◊ Abigail C. Jacobs, Ph.D.
Paul C. Brown, Ph.D.
Center for Devices and Radiological Health
Melvin E. Stratmeyer, Ph.D.
Vasant G. Malshet, Ph.D., D.A.B.T.
Center for Biologics Evaluation and Research
Richard McFarland, Ph.D., M.D.
Ying Huang, Ph.D.
Center for Food Safety and Nutrition
David G. Hattan, Ph.D.
Robert L. Bronaugh, Ph.D.
Center for Veterinary Medicine
Devaraya Jagannath, Ph.D.
M. Cecilia Aguila, D.V.M.
National Center for Toxicological Research
William T. Allaben, Ph.D.
Paul Howard, Ph.D.
Office of Regulatory Affairs
Lawrence D'Hoostelaere, Ph.D.

National Cancer Institute
• Alan Poland, M.D.
◊ T. Kevin Howcroft, Ph.D.

National Institute of Environmental Health Sciences
• William S. Stokes, D.V.M., D.A.C.L.A.M
◊ Raymond R. Tice, Ph.D.
Rajendra S. Chhabra, Ph.D., D.A.B.T.
Jerrold J. Heindel, Ph.D.

National Institute for Occupational Safety and Health
• Paul Nicolaysen, V.M.D.
◊ K. Murali Rao, M.D., Ph.D.

National Institutes of Health
• Margaret D. Snyder, Ph.D.

National Library of Medicine
• Pertti (Bert) Hakkinen, Ph.D.
◊ Jeanne Goshorn, M.S.

Occupational Safety and Health Administration
• Surender Ahir, Ph.D.

[This Page Intentionally Left Blank]

Acknowledgements

The following individuals are acknowledged for their contributions to the evaluation of the reduced LLNA.

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Immunotoxicity Working Group (IWG)

U.S. Consumer Product Safety Commission
Joanna Matheson, Ph.D. (IWG Co-Chair)
Marilyn Wind, Ph.D.

U.S. Environmental Protection Agency
Office of Pesticide Programs
Masih Hashim, D.V.M., Ph.D.
Marianne Lewis
Deborah McCall
Timothy McMahon, Ph.D.
Amy Rispin, Ph.D.
Office of Prevention, Pesticides, and Toxic Substances
Ronald Ward, Ph.D.
Office of Research and Development
Marsha Ward, Ph.D.
Office of Science Coordination and Policy
Karen Hamernik, Ph.D.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Daniel Lyle, Ph.D.
Vasant G. Malshet, Ph.D., D.A.B.T.
Jeffrey Toy, Ph.D.
Center for Drug Evaluation and Research
Paul C. Brown, Ph.D.
Abigail Jacobs, Ph.D. (IWG Co-Chair)
Jiaqin Yao, Ph.D.
Center for Veterinary Medicine
Ruth Barratt, Ph.D., D.V.M.

National Institute of Environmental Health Sciences
Dori Germolec, Ph.D.
William S. Stokes, D.V.M., D.A.C.L.A.M.
Raymond R. Tice, Ph.D.

National Institute for Occupational Safety and Health
B. Jean Meade, D.V.M., Ph.D.

European Centre for the Validation of Alternative Methods — Liaison
Silvia Casati, Ph.D.

Japanese Center for the Validation of Alternative Methods — Liaison
Hajime Kojima, Ph.D.

Reduced Murine Local Lymph Node Assay
Independent Scientific Peer Review Panel
(March 4–6, 2008)

Michael Luster, Ph.D. (Panel Chair)
Senior Consultant to the National Institute for Occupational Safety and Health
Health Effects Laboratory
Morgantown, WV

Nathalie Alépée, Ph.D.
Associate Research Fellow
Pfizer PDRD
MCT Laboratory
Amboise, France

Anne Marie Api, Ph.D.
Vice President, Human Health Sciences
Research Institute for Fragrance Materials
Woodcliff Lake, NJ

Nancy Flournoy, M.S., Ph.D.
Professor and Chair
Department of Mathematics and Statistics
University of Missouri – Columbia
Columbia, MO

Thomas Gebel, Ph.D.
Regulatory Toxicologist
Federal Institute for Occupational Safety & Health
Dortmund, Germany

Sidney Green, Ph.D.*
Professor of Pharmacology
College of Medicine
Howard University
Washington, DC

Kim Headrick, B.Admin., B.Sc.
International Harmonization and Senior Policy Advisor
Policy and Programme Service Office
Health Canada
Ottawa, Ontario, Canada

Dagmar Jírová, M.D., Ph.D.
Toxicologist, Research Manager
Head of Reference Center for Cosmetics and Reference Laboratory for Experimental Immunotoxicology
National Institute of Public Health
Prague, Czech Republic

David Lovell, Ph.D.
Reader in Medical Statistics
Postgraduate Medical School
University of Surrey
Guildford, Surrey, U.K.

Howard Maibach, M.D.
Professor, Department of Dermatology
University of California – San Francisco
San Francisco, CA

James McDougal, Ph.D.
Professor and Director of Toxicology Research
Department of Pharmacology and Toxicology
Boonshoft School of Medicine
Wright State University
Dayton, OH

Michael Olson, Ph.D.
Director of Occupational Toxicology
Corporate Environment, Health and Safety
GlaxoSmithKline
Research Triangle Park, NC

Raymond Pieters, Ph.D.
Associate Professor
Immunotoxicology Group Leader
Institute for Risk Assessment Sciences
Utrecht University
Utrecht, The Netherlands

Jean Regal, Ph.D.
Professor, Department of Pharmacology
University of Minnesota Medical School
Duluth, MN

Jonathan Richmond, MB ChB, FRCSEd*
Head, Animal (Scientific) Procedures Division
Home Office
London, U.K.

Peter Theran, V.M.D.
Consultant
Massachusetts Society for the Prevention of Cruelty to Animals
Novato, CA

Stephen Ullrich, Ph.D.
Professor of Immunology
Graduate School of Biomedical Sciences
University of Texas
M.D. Anderson Cancer Center – Houston
Houston, TX

Michael Woolhiser, Ph.D.
Technical Leader – Immunotoxicology
Senior Toxicology Specialist
Dow Chemical
Midland, MI

Takahiko Yoshida, M.D., Ph.D.
Professor, Department of Health Science
Asahikawa Medical College
Hokkaido, Japan

* Drs. Green and Richmond were unable to attend the public meeting on March 4–6, 2008; however, they took part in the scientific peer review and concur with the conclusions and recommendations included in the *Independent Scientific Peer Review Panel Report - Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products.*

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences

William Stokes, D.V.M., D.A.C.L.A.M.
Director; Project Officer

Raymond Tice, Ph.D.
Deputy Director

Deborah McCarley
Special Assistant; Assistant Project Officer

NICEATM Support Contract Staff (Integrated Laboratory Systems [ILS], Inc.)

David Allen, Ph.D.

Thomas Burns, M.S.

Linda Litchfield

Michael Paris

Eleni Salicru, Ph.D.

Catherine Sprankle

Judy Strickland, Ph.D., D.A.B.T.

Other Acknowledgements

ICCVAM and NICEATM gratefully acknowledge the following individuals and institutions that submitted data to NICEATM used for the evaluation of the rLLNA.

David Basketter, Ph.D.
Unilever Safety and Environmental Assurance Centre
Sharnbrook, U.K.

Phil Botham, Ph.D.
European Crop Protection Association
Brussels, Belgium

Eric Debruyne, Ph.D.
Bayer CropScience SA, Sophia Antipolis
Cedex, France

G. Frank Gerberick, Ph.D.
Procter and Gamble Company
Cincinnati, OH, U.S.

Dori Germolec, Ph.D.
National Toxicology Program
Research Triangle Park, NC, U.S.

Ian Kimber, Ph.D.
Syngenta Central Toxicology Laboratory
Macclesfield, U.K.

Michael J. Olson, Ph.D.
GlaxoSmithKline
Research Triangle Park, NC, U.S.

K. Skirda
TNO Quality of Life
Delft, Netherlands

Peter Ungeheuer, Ph.D.
European Federation for Cosmetic Ingredients
Frankfurt, Germany

Hans Werner Vohr, Ph.D.
Bayer HealthCare
Wuppertal-Elberfeld, Germany

[This Page Intentionally Left Blank]

Preface

In 1998, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in conjunction with the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) evaluated the validation status of the murine local lymph node assay (traditional LLNA) as an alternative to guinea pig test methods (e.g., the Guinea Pig Maximization Test and the Buehler Test) for assessing the allergic contact dermatitis (ACD) potential of substances. ICCVAM subsequently recommended that the LLNA could be used as a valid substitute for the accepted guinea pig test methods in most ACD testing situations (ICCVAM 1999).

Based on the ICCVAM recommendations, the ICCVAM member agencies that require regulatory submission of ACD data accepted the LLNA, with identified limitations, as an alternative to guinea pig tests for assessing the potential of substances to cause ACD. In 2002, the LLNA was adopted as Test Guideline 429 by the 30 member countries of the Organisation for Economic Co-operation and Development (OECD; OECD 2002).

The reduced murine local lymph node assay (rLLNA), also referred to as the "cut-down" or "limit dose" LLNA, was one of several modified versions of the LLNA nominated by the U.S. Consumer Product Safety Commission (CPSC) for evaluation by ICCVAM.[30] (The term "reduced LLNA" has been adopted in this document to be consistent with the terminology used for this test method in Europe.) The proposed rLLNA could reduce the number of animals for skin sensitization testing by 40% for each test compared with the traditional LLNA. ICCVAM assigned this activity a high priority following consideration of comments from the public and ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM).

The ICCVAM Immunotoxicity Working Group (IWG) and NICEATM (1) prepared a draft background review document (BRD) that described the validation status of the rLLNA test method, including its reliability and accuracy, the substances evaluated, and the availability of a standardized protocol and (2) developed draft test method recommendations based on this evaluation. An international independent scientific peer review panel (Panel) met on March 4–6, 2008, to assess the current validation status of the rLLNA. The Panel also reviewed the completeness and accuracy of the draft ICCVAM BRD and the extent to which the information therein supported the ICCVAM draft test method recommendations for proposed test method uses, recommended protocol, test method performance standards, and future studies.

ICCVAM considered the conclusions and recommendations of the Panel, as well as comments received from the public and SACATM, when finalizing ICCVAM's BRD and test method recommendations on the usefulness and limitations of the rLLNA.

We gratefully acknowledge the organizations and scientists who provided data and information for this BRD. We would also like to recognize the efforts of the individuals who contributed to its preparation, review, and revision. We especially recognize the Panel members for their thoughtful evaluations and generous contributions of time and effort. Special thanks are extended to Dr. Michael Luster for serving as the Panel Chair and to Dr. Michael Woolhiser, Dr. Michael Olson, and Ms. Kim Headrick for their service as Evaluation Group Chairs. We

[30] Available at http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf

thank the IWG for assuring a meaningful and comprehensive review. We especially thank Dr. Joanna Matheson (CPSC) and Dr. Abigail Jacobs (U.S. Food and Drug Administration Center for Drug Evaluation and Research) for serving as Co-Chairs of the IWG, as well as the IWG members and ICCVAM representatives who subsequently reviewed the BRD and provided comments.

Integrated Laboratory Systems, Inc., the NICEATM support contractor, provided excellent scientific and operational support for which we thank Dr. David Allen, Mr. Thomas Burns, Ms. Linda Litchfield, Mr. Michael Paris, Dr. Eleni Salicru, Ms. Catherine Sprankle, and Dr. Judy Strickland. We also acknowledge Dr. Raymond Tice, Deputy Director of NICEATM, for his contributions to this project. Finally, we want to thank Dr. Silvia Casati and Dr. Hajime Kojima, the IWG liaisons from the European Centre for the Validation of Alternative Methods and the Japanese Center for the Validation of Alternative Methods, respectively for their participation.

William S. Stokes, D.V.M., D.A.C.L.A.M.
Rear Admiral/Assistant Surgeon General, U.S. Public Heath Service
Director, NICEATM
Executive Director, ICCVAM

Marilyn Wind, Ph.D.
Deputy Associate Executive Director
Directorate for Health Sciences
U.S. Consumer Product Safety Commission
Chair, ICCVAM

Executive Summary

In 1999, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recommended the murine local lymph node assay (traditional LLNA) as a valid substitute for currently accepted guinea pig test methods to assess allergic contact dermatitis (ACD) potential of substances in most ACD testing situations. The recommendation was based on a comprehensive evaluation that included an independent scientific peer review panel (Panel) assessment of the validation status of the LLNA. The Panel report and the ICCVAM recommendations (ICCVAM 1999) are available at the NICEATM–ICCVAM website.[31]

ICCVAM forwarded to U.S. Federal agencies its recommendation that the traditional LLNA should be considered for regulatory acceptance or other non-regulatory applications for assessing the ACD potential of substances, while recognizing that some testing situations would still require the use of traditional guinea pig test methods (ICCVAM 1999). The LLNA was subsequently incorporated into national and international test guidelines for the assessment of skin sensitization (International Organization for Standardization [ISO] 10993-10: Tests for Irritation and Sensitization [ISO 2002]; Organisation for Economic Co-operation and Development Test Guideline [TG] 429 [OECD 2002]; U.S. Environmental Protection Agency Health Effects Test Guideline OPPTS 870.2600: Skin Sensitization [EPA 2003]).

In 2007, the U.S. Consumer Product Safety Commission (CPSC) nominated the rLLNA (also referred to as the "cut-down" or "limit dose" LLNA) as one of several modified versions of the LLNA for evaluation by ICCVAM. The proposed rLLNA could reduce the number of animals for skin sensitization testing by 40% per test compared with the traditional LLNA. The term "reduced LLNA" has been adopted in this document to be consistent with the terminology used for this test method in Europe.

ICCVAM assigned this activity a high priority; and the National Toxicology Program Interagency Committee on the Evaluation of Alternative Methods (NICEATM), along with the ICCVAM Immunotoxicity Working Group (IWG), collaborated closely with liaisons from the European Centre for the Validation of Alternative Methods and the Japanese Center for the Validation of Alternative Methods to facilitate the evaluations requested by the CPSC. NICEATM and the ICCVAM IWG prepared this background review document (BRD), which summarizes the current validation status of the rLLNA for assessing the skin sensitization potential of substances. It includes detailed information about the reliability and relevance of the rLLNA, and the scope of the substances that were evaluated. It provides a comprehensive review of available data and information on the use of the rLLNA for hazard classification.

This information summarized in this BRD is from a retrospective review of traditional LLNA data. The database considered was obtained from 12 different sources and included 457 unique substances[32] tested in a total of 471 traditional LLNA studies. ICCVAM had considered 211 of the substances during its 1998 evaluation of the traditional LLNA (ICCVAM 1999). An additional 246 substances were obtained from the peer-reviewed literature published after that evaluation and from data submitted to NICEATM in response to a 2007 *Federal Register* (*FR*)

[31] Available at http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna/llnarep.pdf

[32] Some substances were tested in more than one vehicle. In such instances, each substance-vehicle combination was considered separately, and thus there were a total of 465 unique substance-vehicle combinations that were used in the performance evaluation.

notice (72 FR 27815, May 17, 2007[33]). Specifically, three sources were published journal articles and eight were responses to the May 2007 *FR* notice. Due to the small number of repeated studies (5% of total studies), all studies were treated independently for the purpose of this accuracy evaluation.

The 1999 ICCVAM-recommended LLNA protocol accepted by U.S. regulatory agencies is consistent with procedures described in OECD TG 429 and was used as the basis for development of the OECD test guideline. Still, TG 429 allows for more procedural variation than the 1999 ICCVAM-recommended protocol (ICCVAM 1999). The protocol for the rLLNA is identical to that for the traditional LLNA (ICCVAM 1999), except that the traditional LLNA tests a substance at three dose levels, with the highest dose level being that which does not induce systemic toxicity and/or excessive skin irritation. In the rLLNA, a substance is tested at only a single dose level, which is the highest dose level that would have been tested in the traditional LLNA. As in the traditional LLNA, the threshold for classifying a substance as a skin sensitizer in the rLLNA is a stimulation index (SI) ≥ 3.

Information on chemical classes for each substance was retrieved from the National Library of Medicine's ChemIDplus® database or assigned for each test substance using a standard classification scheme based on the National Library of Medicine Medical Subject Headings classification system.[34] Chemical class information is included to indicate the variety of structural elements in the evaluated substances. One hundred and twenty-five complex substances were identified simply as pharmaceuticals. Ten substances were formulations. Seventy substances could not be assigned to a specific chemical class due to incomplete information (e.g., no Chemical Abstracts Service Registry Number or structure provided).

The ability of the rLLNA to correctly identify potential skin sensitizers was compared to that of the traditional LLNA. In the 471 studies, 318 detected skin sensitizers, and 153 detected non-sensitizers. When studies for substances tested more than once in the same vehicle (i.e., 465 unique substance and vehicle combinations) were considered together to yield an overall skin sensitization classification, 315 were classified as sensitizers, and 150 were classified as non-sensitizers.

Based on the data available from the 471 studies, the rLLNA has an accuracy of 98.7% (465/471), a sensitivity of 98.1% (312/318), a specificity of 100% (153/153), a false positive rate of 0% (0/153), and a false negative rate of 1.9% (6/318) when compared to the traditional LLNA. Based on the 465 unique substance and vehicle combinations, the rLLNA has an accuracy of 98.7% (459/465), a sensitivity of 98.1% (309/315), a specificity of 100% (150/150), a false positive rate of 0% (0/150), and a false negative rate of 1.9% (6/315).

Six substances yielded false negative results in the rLLNA (i.e., the substances were classified as sensitizers in the traditional LLNA but as non-sensitizers in the rLLNA). A review of the data for these six substances indicates that the traditional LLNA classification of the substances as skin sensitizers was based not on the highest dose level tested, which induced an SI < 3 but on a low- or mid-dose level that produced an SI ≥ 3. Because the rLLNA only tests substances at the highest dose level, all six substances would be incorrectly identified as non-sensitizers (i.e., false negatives). Four of the six substances that resulted in false negatives using the

[33] Available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR_E7_9544.pdf
[34] Available at http://www.nlm.nih.gov/mesh/meshhome.html

rLLNA compared to the traditional LLNA came from LLNA studies that used pooled data. There were no patterns of consistency for these substances with regard to physicochemical properties.

Interlaboratory reproducibility of the rLLNA was assessed with data for five substances tested independently in the same vehicle at multiple laboratories. Among these five substances, three (60%) were classified as sensitizers or non-sensitizers in all studies (i.e., 100% concordance). Each of the other two substances, tested independently in two laboratories, was classified as a sensitizer by one traditional LLNA study and as a non-sensitizer by the other traditional LLNA study. Review of the studies indicates that the discordant results were due to differences in the highest dose levels tested. However, because the traditional LLNA and the rLLNA use identical protocols and the data sets used to evaluate their accuracy are similar, the reliability of the two methods would be expected to be similar. That is, the intra- and interlaboratory reliability of the rLLNA would be expected to be the same as that of the traditional LLNA (see ICCVAM 1999 for these statistics).

A review of published literature on the rLLNA revealed only one published report in addition to that of Kimber et al. (2006). Ryan et al. (2008) described the impact of reducing the number of animals per group from five to two on the performance of the rLLNA and concluded that the sensitivity is inadequate for hazard identification of skin sensitizers.

Compared to the traditional LLNA, the rLLNA will reduce the number of animals used to assess skin sensitization. Because the rLLNA tests only the highest dose level of the test substance in addition to the concurrent control groups, the number of animals tested would decrease by at least 40% for each test.

The database included in this BRD will be updated as additional information becomes available during future use of the traditional LLNA and the rLLNA.

[This Page Intentionally Left Blank]

1.0 Introduction and Rationale for the Proposed Use of the Reduced Murine Local Lymph Node Assay (rLLNA) to Identify Skin Sensitizers

1.1 Introduction

1.1.1 Historical Background

In 1999, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recommended the murine local lymph node assay (traditional LLNA[35]) as a valid substitute for currently accepted guinea pig test methods to assess allergic contact dermatitis (ACD) potential of most types of substances. ICCVAM based its recommendation on a comprehensive evaluation that included an independent scientific peer review panel (Panel) assessment of the validation status of the LLNA. The Panel report and the ICCVAM recommendations (ICCVAM 1999) are available at the NICEATM–ICCVAM website.[36]

ICCVAM forwarded to U.S. Federal agencies its recommendation that the traditional LLNA should be considered for regulatory acceptance or other non-regulatory applications for assessing the ACD potential of substances, while recognizing that some testing situations would still require the use of traditional guinea pig test methods (ICCVAM 1999). The LLNA was subsequently incorporated into national and international test guidelines for the assessment of skin sensitization (International Organization for Standardization [ISO] 10993-10: Tests for Irritation and Sensitization [ISO 2002]; Organisation for Economic Co-operation and Development Test Guideline [TG] 429 [OECD 2002]; U.S. Environmental Protection Agency [EPA] Health Effects Test Guideline OPPTS 870.2600: Skin Sensitization [EPA 2003]).

1.1.2 Allergic Contact Dermatitis

ACD is a frequent occupational health problem. According to the U.S. Department of Labor Bureau of Labor Statistics, in 2005, 980 cases of ACD involved days away from work.[37]

ACD develops in two phases, induction and elicitation. The induction phase occurs when a susceptible individual is exposed topically to a skin-sensitizing substance. Induction depends on the substance passing through the epidermis, where it forms a hapten complex with dermal proteins. Langerhans cells, the resident antigen-presenting cells in the skin, process the hapten complex. The processed hapten complex then migrates to the draining lymph nodes. Antigen presentation to T-lymphocytes follows, which leads to the clonal expansion of these cells. At this point, the individual is sensitized to the substance (Basketter et al. 2003; Jowsey et al. 2006). Studies have shown that the magnitude of lymphocyte proliferation correlates with the extent to which sensitization develops (Kimber and Dearman 1991, 1996).

During the elicitation phase, the individual is again topically exposed to the substance. As in the induction phase, the substance penetrates the epidermis, is processed by the Langerhans cells, and is presented to circulating T-lymphocytes. The T-lymphocytes are then activated, which

[35] The "traditional LLNA" refers to the validated ICCVAM-recommended LLNA (ICCVAM 1999), which measures lymphocyte proliferation based on incorporation of tritiated thymidine into the cells of the draining auricular lymph nodes.
[36] Available at http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna/llnarep.pdf
[37] Available at http://www.bls.gov/IIF

causes release of cytokines and other inflammatory mediators. This release produces a rapid dermal immune response that can lead to ACD (ICCVAM 1999; Basketter et al. 2003; Jowsey et al. 2006).

1.1.3 U.S. Consumer Product Safety Commission (CPSC) Nomination

On January 10, 2007, the CPSC formally requested that ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) evaluate several activities related to the LLNA.[38] The nominated activities included the following:

- The LLNA as a stand-alone assay for potency determination (including severity) for classification purposes
- Non-radioactive LLNA protocols
- The reduced LLNA (rLLNA) (also known as the ‘‘cut-down’’ or ‘‘limit dose’’ LLNA procedure)
- The use of the LLNA to test mixtures, aqueous solutions, and metals

ICCVAM unanimously agreed that the nominated activities should have a high priority for evaluation. ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), also recommended that the nominated activities be undertaken with a high priority.

As ICCVAM and NICEATM collaborate closely with the European Centre for the Validation of Alternative Methods (ECVAM) and the Japanese Center for the Validation of Alternative Methods, both organizations identified liaisons to the ICCVAM Immunotoxicity Working Group to facilitate the evaluations requested by the CPSC.

1.1.4 Description of the Reduced Murine Local Lymph Node Assay

Kimber and colleagues initially discussed the rLLNA in a 2006 publication (Kimber et al. 2006). The rLLNA was also discussed in two posters (Basketter et al. 2007; Chaney et al. 2007, subsequently published as Ryan et al. 2008) and one platform presentation (Basketter 2007) at the Society of Toxicology (SOT) Annual Meeting in Charlotte, NC, on March 25–29, 2007.

The protocol for the rLLNA is identical to that of the traditional LLNA (as described in the 1999 ICCVAM-recommended protocol) with one exception. In the traditional LLNA, three dose levels of each test substance are tested, while in the rLLNA only the highest dose level that does not induce systemic toxicity and/or excessive skin irritation is tested for skin-sensitizing activity (Kimber et al. 2006).

The term “limit dose,” sometimes used to refer to the rLLNA, accurately depicts a modified LLNA that tests only the highest dose level that does not induce local irritation and/or systemic toxicity. The terms “cut-down” and “reduced” LLNA also accurately describe the reduction in the number of doses tested and emphasize the reduction in the number of animals used to perform the test. For consistency with the terminology presented in the publications that first described this version of the LLNA, the term “reduced LLNA” (rLLNA) will be used.

[38] Available at http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf

1.1.5 Results of an ECVAM Peer Review of the rLLNA

The ECVAM Scientific Advisory Committee (ESAC) established a review panel to retrospectively analyze the published LLNA data to determine if limiting the number of test substance dose levels to only the highest dose level could successfully reduce the number of animals used per test. The review was based on the evaluation published by Kimber et al. (2006). At its semi-annual meeting on April 26–27, 2007, ESAC reviewed the rLLNA.

The ESAC statement on the rLLNA, dated April 27, 2007 (**Annex I**), states that:

> "… the peer reviewed and published information is of a quality and nature to support the use of the rLLNA within tiered-testing strategies to reliably distinguish between chemicals that are skin sensitisers and non-sensitisers, and that animal use can be minimised providing:
>
> - The concentration used to evaluate sensitisation potential is the maximum consistent with solubility and the need to avoid local and other systemic adverse effects, and that this principle rather than strict adherence to the specific recommended absolute concentrations as in OECD TG 429 should be used.
> - Negative test results associated with testing using concentrations of less than 10% should undergo further evaluation.
> - Positive and negative (vehicle) control groups are used, as appropriate, per OECD TG 429.
> - The full LLNA should be performed when it is known that an assessment of sensitisation potency is required."

The ESAC statement also recommends "that further work should be undertaken to determine if the 10% concentration threshold referenced above is optimal."

1.2 Regulatory Rationale and Applicability of the rLLNA

Current regulatory testing requires assessment of the potential skin sensitization hazard of regulated substances/products. The rLLNA is being considered for use in identifying skin sensitizers in a weight-of-evidence strategy such as that proposed in the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (U.N. 2005). Unlike the traditional LLNA, the rLLNA evaluates the ability of a substance to be a sensitizer based on testing a single, highest-testable dose level; therefore, dose-response information is not generated. Thus, the rLLNA is being proposed for "yes/no" identification of sensitization hazards.

1.3 Scientific Basis for the rLLNA

1.3.1 Purpose and Mechanistic Basis

The purpose of the rLLNA is to identify potential skin sensitizers by quantifying lymphocyte proliferation in the draining auricular lymph nodes after application of a test substance to the ears of a mouse. The mechanistic basis is identical to that of the traditional LLNA (see **Section 1.1.2**).

1.3.2 Applicability Domain

The applicability domain of the rLLNA should be identical to that of the traditional LLNA. The traditional LLNA was not recommended for the testing of metals, mixtures/extracts, pharmaceuticals, or strong dermal irritants (ICCVAM 1999).

1.4 Test Method Validation

The ICCVAM Authorization Act of 2000 (Sec. 4(c)) mandates that "[e]ach Federal Agency … shall ensure that any new or revised … test method … is determined to be valid for its proposed use prior to requiring, recommending, or encouraging [its use]" (Public Law 106-545, 42 United States Code 285*l*-3).

Validation is the process by which the reliability and relevance of an assay for a specific purpose are established (ICCVAM 1997). *Relevance* is the extent to which an assay will correctly predict or measure the biological effect of interest (ICCVAM 1997). For the rLLNA, relevance is determined by how well the assay identifies (1) substances capable of producing skin sensitization in humans and (2) substances that should be assessed using a diverse set of substances that represent both of the types of chemical and product classes to be tested and the range of responses to be identified.

Reliability is the reproducibility of a test method within and among laboratories. The validation process provides data and information that allow U.S. Federal agencies to develop guidance on the use of test methods in evaluating the skin sensitization potential of substances.

The first stage in this evaluation is the preparation of a draft background review document (BRD) that comprehensively reviews the relevant data and information about a test method, including its mechanistic basis, proposed uses, reliability, and performance characteristics (ICCVAM 1997). The draft BRD is made available to the public and an independent scientific peer review panel (Panel) for review and comment. ICCVAM considers these comments and those of SACATM as they finalize the BRD. ICCVAM provides the final BRD to regulatory agencies for consideration as part of the ICCVAM Test Method Evaluation Report.

1.5 Selection of Citations for the rLLNA BRD

The test method data summarized in this BRD were obtained from the original LLNA evaluation (ICCVAM 1999), peer-reviewed scientific literature, the 2007 SOT Annual Meeting, and responses to a *Federal Register* (*FR*) notice requesting such data (72 FR 27815, May 17, 2007[39]). The terms "reduced LLNA," "cut-down LLNA," "limit dose LLNA," and "limit test LLNA" were used to search MEDLINE®, TOXLINE®, and Web of Science® for publications relevant to the rLLNA test method. A review of these databases through December 2007 revealed two published reports (Kimber et al. 2006; Ryan et al. 2008 [published online ahead of print as Ryan et al. 2007]). The rLLNA was also represented at the 2007 SOT Annual Meeting in two posters (Basketter et al. 2007; Chaney et al. 2007, subsequently published as Ryan et al. 2008) and one platform presentation (Basketter 2007).

[39]Available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR_E7_9544.pdf

2.0 rLLNA Protocol Components

2.1 Overview

The technical aspects of the rLLNA are identical to those of the traditional LLNA; the two methods differ only in the number of test substance dose levels tested (Kimber et al. 2006). In the traditional LLNA, each test substance is tested at a minimum of three dose levels. The highest dose level is the maximum soluble concentration that does not cause systemic toxicity and/or excessive local irritation (ICCVAM 1999). In the rLLNA, in addition to the concurrent vehicle-control group, each test substance is tested at only the highest testable dose level (Kimber et al. 2006).

A Stimulation Index (SI) is calculated as the ratio of radioactivity incorporated into the cells of draining auricular lymph nodes of the treated animals to that of the vehicle-control animals. In both the traditional LLNA and the rLLNA, the threshold for classifying a substance as a skin sensitizer is an SI $\geq$ 3.

2.2 Basis for Test Method Selection

The rLLNA was proposed by Kimber et al. (2006) in an effort to reduce the number of animals used for skin sensitization testing and as a means of streamlining the LLNA for testing that will be required under the Registration, Evaluation and Authorisation of Chemicals regulations (Kimber et al. 2006).

2.3 Proprietary Test Method Components

The rLLNA does not employ any proprietary components.

2.4 Basis for the Number of Mice per Dose Group

The basis for the number of mice per dose group in the rLLNA is the same as that for the traditional LLNA (ICCVAM 1999).

2.5 Study Acceptance Criteria

Similar to the traditional LLNA, in order for an rLLNA study to be considered acceptable, the positive control must yield an SI $\geq$ 3 (ICCVAM 1999).

2.6 Basis for Selection of the Test Substance Dose

As noted in **Section 2.1**, the rLLNA tests each substance at only the highest testable dose level, in addition to the concurrent vehicle control. Consistent with the criteria for selecting the highest dose level in the traditional LLNA (ICCVAM 1999), the dose level used to evaluate sensitization potential in the rLLNA should be the maximum soluble concentration that does not cause systemic toxicity and/or excessive local irritation (ICCVAM 1999).

[This Page Intentionally Left Blank]

3.0 Substances Used for Validation of the rLLNA

3.1 Rationale for the Substances or Products Included in the Evaluation

Data from 471 LLNA studies were obtained from 12 sources (**Table D-1**), including published reports and unpublished data submitted to NICEATM in response to 72 FR 27815.[40]

3.2 Rationale for the Number of Substances Included in the Evaluation

The database from the 471 traditional LLNA studies included 457 unique substances,[41] 211 of which were included in the original ICCVAM evaluation of the traditional LLNA (ICCVAM 1999). Fourteen of the 457 unique substances were tested two to five times each in different LLNA studies. Specifically, nine of the 14 substances were evaluated two to five times in different vehicles, and five of the 14 substances were evaluated two to five times in the same vehicle. Two of the five substances evaluated in the same vehicle (hexyl cinnamic aldehyde [HCA] and potassium dichromate) were also tested using different vehicles (one study for HCA and two studies for potassium dichromate). Due to the small number of repeated studies (5% of total studies), all were treated independently for accuracy evaluation. When the studies for the substances repeated in the same vehicle were considered together to yield an overall skin sensitization classification, there were 465 studies with unique substance–vehicle combinations.

3.3 Detailed Description of Substances Included in the Evaluation

Annex II provides information on the physicochemical properties (e.g., physical form tested), Chemical Abstracts Service Registry Number (CASRN), and chemical class for each substance tested. This information was obtained from the published reports, submitted data, or literature searches.

When available, chemical classes for each substance were retrieved from the National Library of Medicine's ChemIDplus® database. If chemical class information was not located, chemical classes were assigned for each test substance using a standard classification scheme based on the National Library of Medicine Medical Subject Headings.[42] A substance could be assigned to more than one chemical class; however, no substance was assigned to more than three classes. Certain complex pharmaceuticals and pharmaceutical intermediates were simply identified as pharmaceutical substances. Chemical class information is presented only to indicate the variety of structural elements present in the substances evaluated in this analysis; it is not intended to evaluate the impact of structure on skin sensitization activity or potency.

[40] May 17, 2007, available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR_E7_9544.pdf

[41] Some substances were tested in more than one vehicle. In such instances, each substance–vehicle combination was considered separately, thus a total of 465 unique substance–vehicle combinations were evaluated.

[42] Available at http://www.nlm.nih.gov/mesh/meshhome.html

Table D-1 Summary of Traditional LLNA Data Sources and Rationale for Substance Selection

Data Source	Number of Studies	Primary Data Source and Substance Selection Rationale
Gerberick et al. (2005)[1]	210	Compiled from previously conducted studies (published literature and unpublished sources) on substances with varying skin sensitization potential
M.J. Olson/GlaxoSmithKline	124	Pharmaceuticals, pharmaceutical intermediates
Basketter, Gerberick, and Kimber[2]	31	Compiled from previously conducted studies (published literature and unpublished sources) on substances with varying skin sensitization potential
K. Skirda/CESIO (TNO Report V7217)	18	Data were provided by CESIO member companies for use in a paper titled "Limitations of the Local Lymph Node Assay (LLNA) as preferred test for skin sensitisation: concerns about false positive and false negative test results" (TNO report V7217)
Lalko and Api (2006)	17	Original research conducted on essential oils, which were representative of the oils commonly used in perfumery. Each contains significant amounts of one or more known skin sensitizers.
H.W. Vohr/BGIA	16	Original research with epoxy resin components as part of a validation effort for non-radioactive versions of the local lymph node assay
Ryan et al. (2002)	15	Original research with known water-soluble haptens and known skin sensitizers to assess the usefulness of a novel vehicle
D. Germolec/NIEHS	15	Substances evaluated by the National Toxicology Program for skin sensitization potential
E. Debruyne/Bayer CropScience SA	10	Original research on different pesticide types and formulations
P. Ungeheur/EFfCI	9	Data for selected unsaturated chemicals were provided in the report entitled "Comparative Experimental Study on the Skin Sensitising Potential of Selected Unsaturated Chemicals as Assessed by the Murine Local Lymph Node Assay (LLNA) and the Guinea Pig Maximisation Test (GPMT)"
P. Botham/ECPA	6	Plant protection products (i.e., pesticides) were evaluated in the local lymph node assay with a novel vehicle to assess its usefulness
Basketter et al., 2007	1	Original research that re-evaluated resorcinol in the local lymph node assay, which identified resorcinol as a sensitizer.
Total	**471**[3]	

Abbreviations: BGIA = Berufsgenossenschaftliches Institut fur Arbeitsschutz; CESIO = Comite Europeen des Agents de Surface et de Leurs Intermediaires Organiques; ECPA = European Crop Protection Association; EFfCI = European Federation for Cosmetic Ingredients; NIEHS = National Institute for Environmental Health Sciences: TNO = TNO Nutrition and Food Research

[1] These data were submitted to ICCVAM in 1998 for the original evaluation of the validation status of the LLNA (ICCVAM 1999) and were evaluated by the European Centre for the Validation of Alternative Methods (ECVAM) Scientific Advisory Committee in its evaluation of the rLLNA (Gerberick et al. 2005).

[2] Data were included in a submission to ECVAM for the validation of the traditional LLNA as a stand-alone assay for potency determination.

[3] The total number of studies does not take into account the fact that some substances were tested more than once (see **Section 3.2**)

Table D-2 provides chemical class information for the test substances in this rLLNA evaluation. The table distinguishes the chemical classifications of the 211 substances in the original evaluation of the rLLNA (Kimber et al. 2006; ESAC 2007) and the chemical classifications of the additional substances received in response to 72 FR 27815.[43] Of the 211 substances initially evaluated by Kimber et al. (2006), the known chemical classes with the greatest number of substances were carboxylic acids (29) and halogenated hydrocarbons (27). Of the additional 246 substances in this evaluation, the known chemical classes with the greatest number of substances tested were pharmaceutical chemicals (125), carboxylic acids (15), and lipids (14). Ten of the substances included in this evaluation were formulations. Seventy substances could not be assigned to a specific chemical class due to incomplete information (e.g., the lack of a CASRN or structure).

3.4 Coding Procedures

Neither the previous evaluation of these 211 substances (ICCVAM 1999) nor any additional studies used in this evaluation describe coding of substances to avoid potential scoring bias.

Table D-2 Chemical Classes[1] Represented in the Current Traditional LLNA Database

Chemical Class	Number of Substances - Original[2]	Number of Substances - Additional[2]	Chemical Class	Number of Substances - Original	Number of Substances - Additional
Alcohols	9	4	Inorganic Chemicals	0	2
Aldehydes	21	4	Isocyanates	1	0
Amides	4	0	Ketones	5	0
Amidines	1	0	Lactones	2	2
Amines	14	7	Lipids	7	14
Anhydrides	1	0	Macromolecular Substances[3]	0	5
Carbohydrates	3	2	Nitriles	1	1
Carboxylic Acids	29	15	Nitro Compounds	2	0
Esters	3	0	Nitroso Compounds	3	0
Ethers	14	2	Onium Compounds	1	0
Formulations[3]	0	10	Pharmaceutical chemicals[4]	0	125
Heterocyclic Compounds	18	4	Phenols	18	2
Hydrocarbons, Acyclic	2	1	Polycyclic Compounds	5	3
Hydrocarbons, Cyclic	14	7	Quinones	1	1
Hydrocarbons, Halogenated	27	1	Sulfur Compounds	20	2
Hydrocarbons, Other	7	8	Urea	3	0
Imines	0	1	Unknown	28	42

[1] Total number of substances assigned to chemical classes does not equal the total number of substances evaluated because some substances were assigned to more than one class and some substances were not assigned to a specific chemical class.
[2] Number of substances - original represents the substances evaluated in Kimber et al. (2006).
Number of substances - additional represents the substances received in response to 72 FR 27815 (May 17, 2007) (see below)
[3] No chemical class could be assigned. The terms "formulation" or "macromolecular substance" was used to identify these substances.
[4] The chemical classification of "pharmaceutical chemicals" for the GlaxoSmithKline (GSK) substances was suggested by Dr. Michael Olson of GSK to capture three types of pharmaceutical substances (actives, intermediates, and starting materials).

[43] May 17, 2007, available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR_E7_9544.pdf

[This Page Intentionally Left Blank]

4.0 Comparative *In Vivo* Reference Data – the Traditional LLNA

4.1 The Traditional LLNA Protocol Used to Generate Comparative *In Vivo* Reference Data

As described in **Section 2.1**, the traditional LLNA protocol was consistent with the original ICCVAM-recommended protocol (ICCVAM 1999). That original LLNA test method protocol was accepted by U.S. regulatory agencies (e.g., 2003 EPA Health Effects Test Guidelines) and is itself consistent with procedures described in OECD TG 429, having served as the basis for development of the test guideline. Still, TG 429 allows for more procedural variation than the ICCVAM-recommended protocol (ICCVAM 1999).

4.2 Comparative Traditional LLNA Reference Data Used

The traditional LLNA data used to evaluate the rLLNA were obtained from 12 sources (**Table D-1)**. In addition to calculated SI values for each of the tested dose levels, the vehicle tested and values for the estimated concentration needed to produce an SI of 3 (EC3) for substances classified as sensitizers were provided in Gerberick et al. (2005). The data received in response to 72 FR 27815 (May 17, 2007[44]) included calculated SI values for each of the dose levels tested and the vehicle used. If EC3 values were not included in the data source, they were calculated, where possible, using either interpolation or extrapolation (Dearman et al. 2007). This information and the database (by each source) follow in **Annex III**.

4.3 Availability of Original Records for Comparative Traditional LLNA Reference Data

An attempt was made to obtain the original records for the traditional LLNA data through the *FR* notice (72 FR 27815, May 17, 2007[44]) and requests to specific stakeholders. Although the original study records were not obtained for any of the studies, compiled *in vivo* reports and/or transcribed results were obtained and/or are available for all studies included in this evaluation.

4.4 Quality of Comparative Traditional LLNA Reference Data

Good Laboratory Practice (GLP) guidelines are internationally recognized rules designed to produce high-quality laboratory records (OECD 1998; EPA 2006a, 2006b; U.S. Food and Drug Administration [FDA] 2007a). They provide an internationally standardized procedure for the conduct of studies, reporting requirements, archiving of study data and records, and information about the test protocol to ensure the integrity, reliability, and accountability of a study.

Ideally, all data supporting the validity of a test method should be obtained from studies reported and conducted in accordance with GLP guidelines. The extent to which the traditional LLNA studies complied with GLP guidelines is based on the information provided in published and submitted reports. Based on the available information, the following papers and data submissions were identified as originating from studies that followed GLP guidelines or used data obtained according to GLP guidelines:

- H.W. Vohr/Berufsgenossenschaftliches Institut fur Arbeitsschutz (BGIA)

[44] Available at http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/FR/FR_E7_9544.pdf

- P. Ungeheuer/European Federation for Cosmetic Ingredients (EFfCI)
- E. Debruyne/Bayer CropScience SA
- P. Botham/European Crop Protection Association (ECPA)
- M.J. Olson/GlaxoSmithKline (GSK)
- D. Germolec/National Institute for Environmental Health Sciences (NIEHS)

The publication by Gerberick et al. (2005) does not address the GLP compliance of any of the studies discussed. Several of the substances listed in Gerberick et al. (2005) were included in the original LLNA submission to ICCVAM (ICCVAM 1999). According to the submission, "Much of the data used here to support this submission and much of the data contained within the publications cited in this document have been derived from audited Good Laboratory Practice (GLP) compliant studies. Where this is not the case all investigations have been conducted to the spirit of GLP or Good Research Practice in GLP compliant facilities" (reproduced in ICCVAM 1999). Furthermore, in response to requests from ICCVAM, records were provided indicating compliance with GLP guidelines for some of the studies.

4.5 Accuracy and Reliability of the Traditional LLNA

4.5.1 Accuracy

ICCVAM (1999) reviewed the performance of the traditional LLNA with comparisons to (1) the Guinea Pig Maximization Test and the Buehler Test (EPA 2003) and (2) human results obtained from the human maximization test[45] and human patch test allergen[46] panels. The evaluation concluded that the LLNA demonstrated adequate accuracy (ICCVAM 1999).

4.5.2 Reliability

ICCVAM (1999) also reviewed the reliability of the traditional LLNA as assessed by intra- and interlaboratory reproducibility. The evaluation concluded that the LLNA demonstrated adequate intra- and interlaboratory repeatability and reproducibility (ICCVAM 1999).

[45] The human maximization test involves application of occluded patches on the same skin site with a rest period between each reapplication. Two weeks after the last induction patch, sensitization is evaluated using a 48-hour occluded patch test. The site is scored 24 and 48 hours after patch removal.

[46] Allergen patch tests are diagnostic tests applied to the surface of the skin to identify the cause of contact dermatitis. Chemicals and substances included in these tests (e.g., nickel, rubber, and fragrance mixes) are known to cause contact dermatitis (i.e., skin sensitization) (http://www.fda.gov/cber/allergenics.htm).

5.0 rLLNA Test Method Data and Results

5.1 Description of the rLLNA Test Method Protocol Used to Generate Data

No specific rLLNA studies were conducted for this evaluation; rather, data from traditional LLNA studies were evaluated retrospectively. The only difference in the test method protocols between the traditional LLNA and the rLLNA is the number of dose levels tested. In the traditional LLNA, at least three test-substance dose levels are tested, with the highest dose level based on maximum solubility and the avoidance of systemic toxicity and/or excessive local irritation. In contrast, only the highest dose level of a substance is tested in the rLLNA (Kimber et al. 2006). This retrospective evaluation assumes that the top dose level tested in the traditional LLNA studies was in fact the maximum soluble concentration that did not cause overt systemic toxicity and/or excessive local irritation. Because the criteria for choosing the top dose in the traditional LLNA and in the rLLNA are the same, the maximum dose level tested should be the same for both. However, it is important to consider that the highest possible dose level selected in a prospective validation study may differ between the two versions of the LLNA. Thus, the accuracy analysis of these same substances in a prospective rLLNA study may differ from the accuracy analysis obtained in this retrospective rLLNA analysis.

5.2 Availability of Original rLLNA Data Used to Evaluate Accuracy and Reliability

While original study records were not obtained for any of the previously conducted studies, compiled *in vivo* reports and/or transcribed results were obtained and/or available for all studies included in this evaluation.[47]

5.3 Description of the Statistical Procedure Used to Evaluate rLLNA Data

The performance analysis in this BRD focuses on the ability of the rLLNA to identify potential skin sensitizers as determined by the calculated SI for each test substance (see **Section 2.1**).

5.4 Summary of Results

The data evaluated here were obtained from 12 sources (**Table D-1**). Where available, the specific information extracted for each substance includes its name, CASRN, physicochemical properties (e.g., form tested, Log K_{ow}), and chemical class[48] (**Annex II**). Dose levels tested, along with calculated SI and/or EC3 values, sensitizing hazard classification, and the data source are provided in **Annex III**. If EC3 values were not included in the data source, they were calculated, where possible, using either interpolation or extrapolation (Dearman et al. 2007). Other than the information provided in the submitted data, no additional attempt was made to identify the source or purity of the test substance.

[47] The LLNA data for several of the substances evaluated for this report were included in the database that was submitted to ICCVAM in 1998 for the initial evaluation of LLNA (ICCVAM 1999). Therefore, some of the original data for these substances were available for review.

[48] Chemical classes were assigned by NICEATM based on the classification of the National Library of Medicine's Medical Subject Heading (available at http://www.nlm.nih.gov/mesh/meshhome.html).

5.5 Use of Coded Substances

Neither the previous evaluation of these 211 substances (ICCVAM 1999) nor any additional studies used in this evaluation describe coding of substances to avoid potential scoring bias.

5.6 Lot-to-Lot Consistency of Test Substances

Ideally, a single lot of each substance is used during the validation of a test method. In situations where multiple lots of a chemical must be used, the lot-to-lot consistency of a test substance must be evaluated to ensure the consistency of the substance evaluated over the course of the study. The procedures used to evaluate lot-to-lot consistency are described in the published reports. No attempt was made to review original records to assess the procedures used to evaluate different batches.

Data submitted by P. Botham/ECPA, P. Ungheuer/EFfCI, and D. Germolec/NIEHS included the source and the batch number of each tested substance.

5.7 Availability of Original Data for External Audit

The LLNA data included in the ICCVAM (1999) database were reviewed during the original evaluation. The original data for the other studies included in this evaluation were not available.

6.0 Accuracy of the rLLNA

6.1 Performance Statistics

A critical component of a formal evaluation of the validation status of a test method is an assessment of the accuracy of the proposed tested method when compared to the current reference test method (ICCVAM 2003). This aspect of assay performance is typically evaluated by calculating:

- *Accuracy* (concordance): the proportion of correct outcomes (positive and negative) of a test method
- *Sensitivity*: the proportion of all positive substances that are classified as positive
- *Specificity*: the proportion of all negative substances that are classified as negative
- *Positive predictivity*: the proportion of correct positive responses among substances testing positive
- *Negative predictivity*: the proportion of correct negative responses among substances testing negative
- *False positive rate*: the proportion of all negative substances that are falsely identified as positive
- *False negative rate*: the proportion of all positive substances that are falsely identified as negative

The ability of the rLLNA to correctly identify potential skin sensitizers was compared to that of the traditional LLNA for 471 studies.[49] Of the 471 studies, 318 detected skin sensitizers and 153 detected non-sensitizers.[50] Classification of substances and complete data for each substance are located in **Annex III**. When studies for the substances tested more than once in the same vehicle were considered together to yield an overall skin sensitization classification, 465 unique substance–vehicle combination studies resulted. Of these, 315 detected sensitizers and 150 detected non-sensitizers.

Based on the available study data, the rLLNA has an accuracy of 98.7% (465/471), a sensitivity of 98.1% (312/318), a specificity of 100% (153/153), a false positive rate of 0% (0/153), and a false negative rate of 1.9% (6/318) when compared to the traditional LLNA. When substances tested more than once in the same vehicle were considered together, the resulting 465 studies give an accuracy of 98.7% (459/465), a sensitivity of 98.1% (309/315), a specificity of 100% (150/150), a false positive rate of 0% (0/150), and a false negative rate of 1.9% (6/315). The performance characteristics of the rLLNA as discussed in Kimber et al. (2006) are presented in **Table D-3**.

[49] Due to the small number of repeated studies (5%), all studies were treated independently for this accuracy evaluation. When the studies for the substances repeated in the same vehicle were considered together to yield an overall skin sensitization classification, there were 465 studies with unique substance–vehicle combinations.

[50] For two of the repeated studies (HCA and linalool alcohol), the LLNA obtained discordant results. In both cases, one study classified the substance as a non-sensitizer and the other classified it as a sensitizer. Review of the studies indicates differences in the highest dose levels tested. For each of the studies, the traditional LLNA and the rLLNA both classified the substance as a sensitizer or as a non-sensitizer.

Table D-3 Performance of the rLLNA in Predicting Skin Sensitizers Compared to the Traditional LLNA

Data	N	Accuracy		Sensitivity		Specificity		Positive Predictivity		Negative Predictivity		False Positive		False Negative	
		%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Kimber et al. (2006)	211	98.6	208/211	98.2	166/169	100	42/42	100	166/166	93.3	42/45	0	0/42	1.8	3/169
rLLNA	471	98.7	465/471	98.1	312/318	100	153/153	100	312/312	96.2	153/159	0	0/153	1.9	6/318
rLLNA - substances repeated in the same vehicle were considered together	465	98.7	459/465	98.1	309/315	100	150/150	100	309/309	96.2	150/156	0	0/150	1.9	6/315

Abbreviations: N = number of studies; No. = numbers used to calculate percentage

Kimber et al. (2006) proposed that a minimum testing concentration be considered for the purpose of judging the appropriateness of a non-sensitizing classification for a test substance. In their evaluation, Kimber et al. proposed testing a minimum concentration of 10% in a dose solution (2006). However, lack of sensitizing potential at 10% does not necessarily indicate that a substance will not elicit skin sensitization when tested at a higher concentration. In fact, 51 substances (16% [51/315]) within the current database were non-sensitizers at concentrations of 10%[51] but were sensitizers at higher concentrations (see **Annex IV**).

According to the 1999 ICCVAM-recommended LLNA protocol, the maximum concentration tested should be "the highest achievable level while avoiding overt systemic toxicity and/or excessive local irritation." Similar text is included in OECD TG 429 (2002). Thus, setting a minimum testing concentration is not advised because the maximum soluble concentration that avoids systemic toxicity and/or excessive local irritation may be less than 10% with a non-sensitizing result.

6.2 Discordant Results

In the current analysis, six substances yielded false negative results in the rLLNA. The discordant substances were 2-methyl-2H-isothiazol-3-one, C19-azlactone, azithromycin, camphorquinone, nickel sulfate, and a substance designated as non-ionic surfactant 2. A review of the data for the false negatives indicates that the traditional LLNA classification of the substances as skin sensitizers was based on a low- or mid-dose level that produced an SI ≥ 3, while the highest dose level tested produced an SI < 3 (see **Table D-4**). Because the rLLNA evaluates only the highest dose level tested, all six substances were identified as non-sensitizers (i.e., false negatives). Four of the six substances that resulted in false negatives using the rLLNA compared to the traditional LLNA came from LLNA studies that used pooled data. Graphs of the dose-response curves for these six substances are provided in **Figure D-1**.

Table D-4 Traditional LLNA Data for Substances Identified as False Negatives by the rLLNA

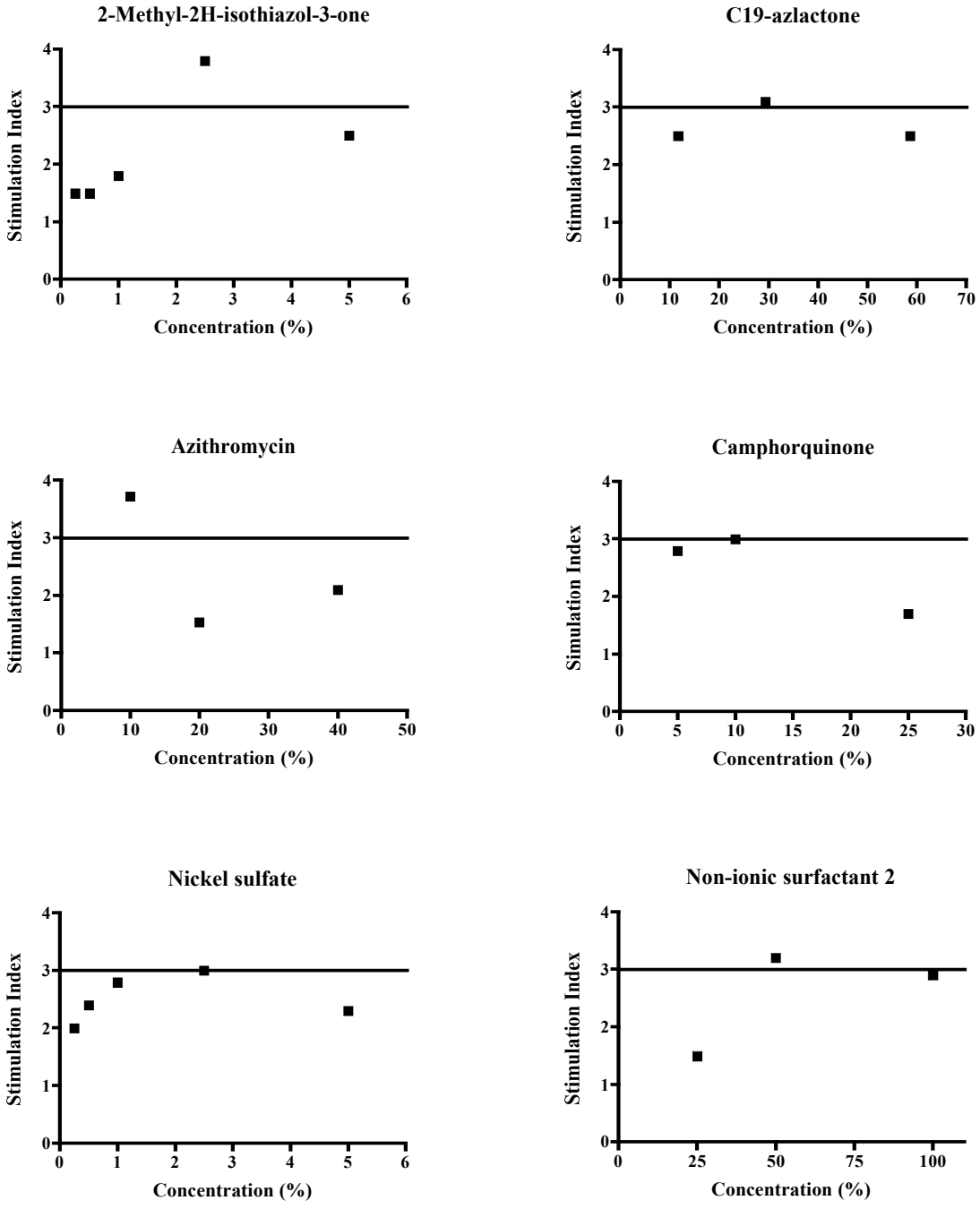
Substance	Vehicle	EC3	Traditional LLNA Data (Low- or Mid-Dose Level)		Traditional LLNA Data (Highest Dose Level)	
			Dose (%)	SI	Dose (%)	SI
2-methyl-2H-isothiazol-3-one	AOO	1.9	2.5	3.8	5	2.5
C19-azlactone	AOO	26	29.33	3.1	58.67	2.5
Azithromycin	Acetone	NC[1]	10	3.7	40	2.1
Camphorquinone	AOO	10	10	3.0	25	1.7
Nickel sulfate	Pluronic L92 (1%)	2.5	2.5	3.0	5	2.3
Non-ionic surfactant 2	AOO	47.1	50	3.2	100	2.9

Abbreviations: AOO = acetone: olive oil (4:1 by volume); EC3 = estimated concentration needed to produce a stimulation index of 3; NC = not calculated; SI = stimulation index

[1] Data was not calculated because extrapolation between points that bracket an SI of 3 could not be done.

[51] An initial dose was tested at a concentration of 10% or greater and resulted in an SI < 3, while a subsequent higher concentration resulted in an SI ≥ 3.

Figure D-1 Dose-Response Curves for Substances Identified as Sensitizers by the Traditional LLNA but as Non-Sensitizers by the rLLNA



Note: The horizontal line in each figure indicates a stimulation index of 3, which is the threshold for a positive response in the LLNA. Points on or above this line would indicate a positive (sensitizer) response, while points below this line would indicate a negative (non-sensitizer) response.

Table D-5 provides a summary of the available physicochemical properties of these substances and the vehicle used.

Table D-5 Summary of Available Physicochemical Properties for False Negatives, as Identified by the rLLNA

Substance	CASRN	Vehicle	Molecular Weight (g/mol)	K_{OW}[1]
2-Methyl-2H-isothiazol-3-one	2682-20-4	AOO	115.15	0.68[2]
C19-azlactone	—	AOO	379.63	5.21[2]
Azithromycin	83905-01-5	Acetone	748.99	3.24[3]
Camphorquinone	465-29-2	AOO	166.22	2.15[2]
Nickel sulfate	7786-81-4	Pluronic L92 (1%)	154.76	-0.17[3]
Non-ionic surfactant 2	—	AOO	—	—

Abbreviations: AOO = acetone: olive oil (4:1 by volume); CASRN = Chemical Abstracts Service Registry Number

[1] K_{OW} represents the octanol-water partition coefficient (expressed on log scale).

[2] K_{OW} calculated by the method of Moriguchi et al. (1994) and provided in Gerberick et al. (2005).

[3] K_{OW} calculated by the method of Meylan and Howard (1995) and obtained from the web site http://www.srcinc.com/what-we-do/databaseforms.aspx?id=385

[This Page Intentionally Left Blank]

7.0 Reliability of the rLLNA

An assessment of test method reliability (intralaboratory repeatability and intra- and interlaboratory reproducibility) is essential to evaluate the performance of an alternative test method (ICCVAM 2003). *Repeatability* refers to the closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period (ICCVAM 1997, 2003). *Intralaboratory reproducibility* refers to the determination of the extent to which qualified personnel within the same laboratory can replicate results using a specific test protocol at different times. *Interlaboratory reproducibility* refers to the determination of the extent to which different laboratories can replicate results using the same protocol and test substances, and indicates the extent to which a test method can be transferred successfully among laboratories.

In the data review, interlaboratory reproducibility of the rLLNA could be assessed with traditional LLNA data available for only five substances that had been tested in the same vehicle at multiple labs (**Annex III**). These are dinitrochlorobenzene (DNCB), HCA, linalool alcohol, methyl salicylate, and potassium dichromate. **Table D-6** provides a summary of the responses obtained by the rLLNA. Among these five substances, tested independently in two to three laboratories, DNCB, methyl salicylate, and potassium dichromate (3/5 = 60%) were classified as sensitizers or non-sensitizers in all studies (i.e., 100% concordance). For the other two substances, HCA and linalool alcohol, tested independently in two laboratories, one traditional LLNA study indicated each substance as a sensitizer and the other traditional LLNA study indicated each substance as a non-sensitizer.

Review of the studies indicates that the discordant results were due to differences in the highest dose levels tested. However, because the rLLNA and traditional LLNA use identical protocols and use similar data sets to evaluate the accuracy of the rLLNA and traditional LLNA, the reliability of the two methods would be expected to be similar. That is, the intra- and interlaboratory reliability of the rLLNA would be expected to be similar to that of the traditional LLNA (see ICCVAM 1999 for these statistics).

Table D-6 rLLNA Responses for Repeated Studies

Substance	Data Source	Vehicle	Traditional LLNA Response in Multiple Studies						rLLNA Classification [1]
			Dose (%)/SI	Dose (%)/SI	Dose (%)/SI	Dose (%)/SI	Dose (%)/SI	Dose (%)/SI	
1-Chloro-2-dinitrobenzene	Gerberick et al. (2005)	AOO	0.01/1.50	0.025/1.80	0.05/2.40	0.1/8.90	0.25/38.00	NA	+
	Data submitted by D. Germolec		0.01/1.17	0.025/1.12	0.05/1.93	0.1/1.95	0.25/7.10	NA	+
Hexyl cinnamic aldehyde	Gerberick et al. (2005)	AOO	2.5/1.30	5/1.10	10/2.50	25/10.00	50/17.00	NA	+
	Data Submitted by H.W. Vohr		2.5/1.10	5/1.20	10/2.84	NA	NA	NA	-
Linalool alcohol	Gerberick et al. (2005)	AOO	NA	NA	NA	25/2.50	50/4.80	100/8.30	+
	Data Submitted by D. Basketter, I. Kimber, and F. Gerberick		1/1.00	10/1.30	30/1.30	NA	NA	NA	-
Methyl salicylate	Gerberick et al. (2005)	AOO	1/1.00	2.5/1.10	5/1.60	10/1.40	20/0.90	NA	-
	Data submitted by D. Germolec		1/0.86	2.5/1.19	5/1.16	10/1.41	20/1.72	NA	-
Potassium dichromate	Gerberick et al. (2005)	DMSO	0.025/1.60	0.05/1.40	0.1/3.80	0.25/5.30	0.5/16.10	NA	+
	Data submitted by D. Germolec		0.025/1.21	0.05/1.84	0.1/2.22	0.25/3.39	NA	NA	+
	Ryan et al. (2002)		0.025/1.40	0.05/2.50	0.1/9.50	0.25/25.90	0.5/10.10	NA	+

Abbreviations: AOO = acetone: olive oil; DMSO = dimethyl sulfoxide; NA = not applicable because dose level was not tested; SI = stimulation index

[1] - = non-sensitizer, + = sensitizer

8.0 rLLNA Data Quality

8.1 Adherence to National and International GLP Guidelines

The extent to which the LLNA studies complied with GLP guidelines is based on the information provided in published and submitted reports. Based on the available information, the following papers and data submissions were identified as originating from studies that followed GLP guidelines or used data obtained according to GLP guidelines: H.W. Vohr/BGIA, P. Ungeheuer/EFfCI, E. Debruyne/Bayer CropScience SA, P. Botham/ECPA, M.J. Olson/GSK, and D. Germolec/NIEHS.

8.2 Data Quality Audits

Formal assessments of data quality, such as quality assurance audits, generally involve a systematic and critical comparison of the data provided in a study report to the laboratory records generated for a study.

Much of the data published by Gerberick et al. (2005) was conducted following GLP guidelines or were conducted in GLP-compliant facilities. Therefore, it was previously inferred that data audits were conducted on the data (ICCVAM 1999).

A formal assessment of the quality of the remainder of the LLNA data included in this BRD was not feasible. The published data on the LLNA were limited to tested concentrations and calculated SI and EC3 values. Auditing the reported values would require obtaining the original individual animal data for each LLNA experiment, which were not obtained. However, the conduct of many of the studies according to GLP guidelines implies that an independent quality assurance audit was conducted.

8.3 Impact of Deviations from GLP Guidelines

The impact of deviations from GLP guidelines cannot be evaluated for the data reviewed in this BRD, because no information on data quality audits was obtained.

8.4 Availability of Laboratory Notebooks or Other Records

The original records were not obtained for the studies included in this evaluation. Data were available for several of the substances included in the ICCVAM 1999 evaluation, thus some of the raw data for these substances were available for review.

[This Page Intentionally Left Blank]

9.0 Other rLLNA Scientific Reports and Reviews

9.1 Reports in the Peer-Reviewed Literature

A search of the terms "reduced LLNA," "cut-down LLNA," "limit dose LLNA," and "limit test LLNA" in the MEDLINE®, TOXLINE®, and Web of Science® search engines through December 2007 produced one relevant published report in addition to that of Kimber et al. (2006). Three related presentations (two posters and one platform) were included in the 2007 SOT Annual Meeting held in Charlotte, NC, from March 25-29. One of the posters (Basketter et al. 2007) and the platform presentation (Basketter 2007) detailed the evaluation that resulted in the Kimber et al. (2006) publication and are therefore not discussed below. The information in the second poster, Chaney et al. (2007), described the impact of reducing the number of animals per dose group on the performance of the rLLNA and is summarized below from the subsequent publication (Ryan et al. 2008; published online ahead of print as Ryan et al. 2007).

9.1.1 Ryan et al. (2008)

Ryan et al. (2008) evaluated the impact of reducing the number of mice (from five animals to two) on the performance characteristics using the rLLNA. Nineteen sensitizing and five non-sensitizing sustances were evaluated with 33 sensitizer datasets and eight non-sensitizer data sets.

SI values were determined for all possible two-animal combinations for the control- and high-dose groups. With 10 possible data combinations per experimental group, there were 100 possible sets of four values (two control animals and two high-dose animals) for each data set. The 100 possible SI values, each based on a unique set of four values, were plotted for each data set, and the percentage of combinations that resulted in an SI $\geq$ 3 was calculated. Of the sensitizers evaluated, at least 96% of the combinations yielded an SI $\geq$ 3 for 76% (25/33) of the data sets. Thirteen or fewer percent ($\leq$13%) of the possible combinations of non-sensitizers (excluding three data sets for sodium lauryl sulfate) had an SI $\geq$ 3. For the data sets with threshold SI values (2–4.9), however, 90% or more of the combinations resulted in SI $\geq$ 3 for only 20% (4/20) of the sensitizers. Thirteen of the 20 (65%) sensitizer data sets had less than 75% of the combinations producing SI $\geq$ 3. The authors concluded that the decreased sensitivity produced by using two mice per group was inappropriate for using the rLLNA to identify skin sensitization hazard.

[This Page Intentionally Left Blank]

10.0 Animal Welfare Considerations

10.1 How the rLLNA will Refine, Reduce, or Replace Animal Use

Compared to the traditional LLNA, the rLLNA will reduce the number of animals used to assess skin sensitization. In addition to a concurrent vehicle-control group and a positive-control group, the traditional LLNA requires testing four to five mice with each of at least three test-substance dose levels (ICCVAM 1999). Because the rLLNA tests only the highest dose level of the test substance being evaluated, in addition to the concurrent control groups, the number of animals tested would be decreased by at least 40% for each test.

10.2 Requirements for the Use of Animals

The rationale for the use of animals and the basis for determining the number of animals used in the rLLNA are the same as those for the traditional LLNA (ICCVAM 1999).

[This Page Intentionally Left Blank]

11.0 Practical Considerations

Several issues in addition to performance evaluations must be taken into account when assessing the practicality of an alternative test method in comparison to the existing test method:

- Assessments of the laboratory equipment and supplies needed to conduct the alternative test method
- Level of personnel training
- Labor costs
- Time required to complete the test method

The time, personnel cost, and effort required to conduct the proposed test method(s) must be considered reasonable in comparison to those of the test method it is intended to replace.

11.1 Transferability of the rLLNA

Test method transferability addresses the ability of a method to be performed accurately and reliably by multiple laboratories (ICCVAM 2003), including those experienced in the particular type of procedure as well as laboratories with less or no experience in the particular procedure. The degree of transferability of a test method can be evaluated by its interlaboratory reproducibility. **Section 7.0** discusses the minimum variability expected. The transferability of the rLLNA is equal to that of the traditional LLNA (ICCVAM 1999), which includes considerations for the required facilities, major fixed equipment, and any other necessary supplies.

11.2 rLLNA Training Considerations

The level of training and expertise needed to conduct the rLLNA, and the training requirements needed to demonstrate proficiency, are identical to that for the traditional LLNA (ICCVAM 1999).

11.3 Cost Considerations

The rLLNA uses the same basic protocol as the traditional LLNA. However, because fewer animals are tested, the related test costs (e.g., animal care, radioactivity, scintillation fluid, etc.) would be expected to be proportionally lower than the traditional LLNA.

11.4 Time Considerations

Because at least 40% fewer animals are tested in the rLLNA than in the traditional LLNA, the overall time required to conduct the method (e.g., dosing mice, removing the auricular lymph nodes from the animals) would be expected to decrease proportionally.

[This Page Intentionally Left Blank]

12.0 References

Basketter D, Patlewicz G, Gerberick F, Ryan C, Kern P, Betts C, et al. 2007. Identification of skin sensitizing chemicals in a reduced LLNA. [Abstract]. Toxicologist 96:236.

Basketter DA. 2007. Integrated systems and a modified local lymph node assay [Abstract]. Toxicologist 96:124.

Basketter DA, Sanders D, Jowsey IR. 2007. The skin sensitization potential of resorcinol: Experience with the local lymph node assay. Contact Dermatitis 56:196–200.

Basketter DA, Smith Pease CK, Patlewicz GY. 2003. Contact allergy: The local lymph node assay for the prediction of hazard and risk. Clin Exp Dermatol 28:218–221.

Chaney J, Ryan C, Kern P, Patlewicz G, Basketter D, Betts C, et al. 2007. The impact of reducing animal numbers in the local lymph node assay. [Abstract]. Toxicologist 96:236.

Dearman RJ, Betts CJ, Farr C, McLaughlin J, Berdasco N, Wiench K, et al. 2007. Comparative analysis of skin sensitization potency of acrylates (methyl acrylate, ethyl acrylate, butyl acrylate, and ethylhexyl acrylate) using the local lymph node assay. Contact Dermatitis 57:242–247.

EPA. 2003. Health Effects Test Guideline, OPPTS 870.2600. Skin Sensitization EPA 712–C–03–197. Washington, DC: U.S. Environmental Protection Agency. Available: http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Revised/870r-2600.pdf.

EPA. 2006a. Good Laboratory Practice Standards. Toxic Substances Control Act. 40 CFR 792. Available: http://www.access.gpo.gov/nara/cfr/waisidx_06/40cfr792_06.html.

EPA. 2006b. Good Laboratory Practice Standards. Federal Insecticide, Fungicide, and Rodenticide Act. 40 CFR 160. http://www.access.gpo.gov/nara/cfr/waisidx_06/40cfr160_06.html.

ESAC. 2007. Statement on the Reduced Local Lymph Node Assay (rLLNA). European Commission Directorate General, Joint Research Centre, Institute for Health and Consumer Protection, European Centre for the Validation of Alternative Methods, April 2007. Available: http://ecvam.jrc.it/ft_doc/ESAC26_statement_rLLNA_20070525-1.pdf

FDA. 2007a. Good laboratory practice for nonclinical laboratory studies. 21 CFR 58.

Gerberick GF, Ryan CA, Kern PS, Schlatter H, Dearman RJ, Kimber I, et al. 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16:157–202.

ICCVAM. 1997. Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH Publication No.: 97-3981. Research Triangle Park, NC: National Institute of Environmental Sciences. Available: http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf.

ICCVAM 1999. The Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemical/Compounds. NIH Publication No. 99-4494. Research Triangle Park, NC: National Institute of Environmental Sciences. Available: http://iccvam.niehs.nih.gov/docs/immunotox_docs/llna/llnarep.pdf.

ICCVAM. 2003. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. NIH Publication No: 03-4508. Research Triangle Park, NC: National Institute of Environmental Sciences. Available: http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.pdf.

ICCVAM Authorization Act. 2000. Public Law 106-545, 42 U.S.C. 285*l*-3. Available: http://iccvam.niehs.nih.gov/docs/about_docs/PL106545.pdf.

ISO. 2002. Biological evaluation of medical devices -- Part 10: Tests for irritation and delayed-type hypersensitivity. Available for purchase at: http://www.iso.org/iso/home.htm.

Jowsey IR, Basketter DA, Westmoreland C, Kimber I. 2006. A future approach to measuring relative skin sensitising potency: a proposal. J Appl Toxicol 26:341–350.

Kimber I, Dearman RJ. 1991. Investigation of lymph node cell proliferation as a possible immunological correlate of contact sensitizing potential. Food Chem Toxicol 29:125–129.

Kimber I, Dearman RJ. 1996. Contact hypersensitivity: immunological mechanisms. In: Toxicology of Contact Hypersensitivity (Kimber I, Maurer T, eds). London: Taylor and Francis, 4–25.

Kimber I, Dearman RJ, Betts CJ, Gerberick GF, Ryan CA, Kern PS, et al. 2006. The local lymph node assay and skin sensitization: a cut-down screen to reduce animal requirements? Contact Dermatitis 54:181–185.

Lalko J, Api AM. 2006. Investigation of the dermal sensitization potential of various essential oils in the local lymph node assay. Food Chem Toxicol 44:739–746.

Meylan WM, Howard PH. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J Pharm Sci 84:83–92.

Moriguchi I, Hirono S, Nakagome I, Hirano H. 1994. Comparison of reliability of log P values for drugs calculated by several methods. Chem Pharm Bull 42:976–978.

OECD. 1998. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). ENV/MC/CHEM (98)17. Paris: OECD.

OECD. 2002. Test No. 429. Skin Sensitisation: Local Lymph Node Assay. Adopted April 24, 2002. In: OECD Guidelines for Testing of Chemicals. Paris: OECD. Available: http://oberon.sourceoecd.org/vl=2675708/cl=14/nw=1/rpsv/cgi-bin/fulltextew.pl?prpsv=/ij/oecdjournals/1607310x/v1n4/s30/p1.idx.

Ryan CA, Chaney JG, Kern PS, Patlewicz GY, Basketter DA, Betts CJ, et al. 2008. The reduced local lymph node assay: the impact of group size. J Appl Toxicol 28:518–523.

Ryan CA, Cruse LW, Skinner RA, Dearman RJ, Kimber I, Gerberick GF. 2002. Examination of a vehicle for use with water soluble materials in the murine local lymph node assay. Food Chem Toxicol 40:1719–1725.

U.N. 2005. Globally Harmonised System of Classification and Labelling of Chemicals (GHS). Geneva: United Nations Publications.

[This Page Intentionally Left Blank]

13.0 Glossary

Accuracy: (a) The closeness of agreement between a test method result and an accepted reference value. (b) The proportion of correct outcomes of a test method. It is a measure of test method performance and one aspect of *relevance*. The term is often used interchangeably with *concordance* (see also *two-by-two table*). Accuracy is highly dependent on the prevalence of positives in the population being examined.*

Allergic contact dermatitis (ACD): A Type IV allergic reaction of the skin that results from repeated skin contact with a skin sensitizer. Clinical signs include the development of erythema (redness) and edema (swelling), blistering, and itching. Also referred to as *skin sensitization*.

Assay: The experimental system used. Often used interchangeably with *test* and *test method*.*

Coded substances: Substances labeled by code rather than name so that they can be tested and evaluated without knowledge of their identity or anticipation of test results. Coded substances are used to avoid intentional or unintentional bias when evaluating laboratory or test method performance.

Concordance: The proportion of all substances tested that is correctly classified as positive or negative. It is a measure of test method performance and one aspect of *relevance*. The term is often used interchangeably with *accuracy* (see also *two-by-two table*). Concordance is highly dependent on the prevalence of positives in the population being examined.*

EC3: The estimated concentration needed to produce a stimulation index of 3, as compared to the concurrent vehicle control.

Essential test method component: Structural, functional, and procedural elements of a test method that are used to develop the test method protocol. These components include unique characteristics of the test method, critical procedural details, and quality control measures. Adherence to essential test method components is necessary when the acceptability of a proposed test method is being evaluated based on performance standards derived from mechanistically and functionally similar validated test method. [Note: Previously referred to as *minimum procedural standards.*]*

False negative: A substance incorrectly identified as negative by a test method.*

False negative rate: The proportion of all positive substances falsely identified by a test method as negative (see *two-by-two table*). It is one indicator of test method accuracy.*

False positive: A substance incorrectly identified as positive by a test method.*

False positive rate: The proportion of all negative substances that are falsely identified by a test method as positive (see *two-by-two table*). It is one indicator of test method accuracy.*

Good Laboratory Practices (GLP): Regulations promulgated by the U.S. Food and Drug Administration and the U.S. Environmental Protection Agency, and principles and procedures adopted by the OECD and Japanese authorities, which describe record keeping and quality assurance procedures for laboratory records that will be the basis for data submissions to national regulatory agencies.*

The definitions in this glossary are restricted to their uses with respect to the rLLNA and the traditional LLNA.

* Definition used by ICCVAM (ICCVAM 2003).

Hazard: The potential for an adverse health or ecological effect. Hazard potential results only if an exposure occurs that leads to the possibility of an adverse effect being manifested.*

Interlaboratory reproducibility: A measure of whether different qualified laboratories using the same protocol and test substances can produce qualitatively and quantitatively similar results. Interlaboratory reproducibility is determined during the prevalidation and validation processes and indicates the extent to which a test method can be transferred successfully among laboratories.*

Intralaboratory repeatability: The closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period.*

Intralaboratory reproducibility: The first stage of validation; a determination of whether qualified people within the same laboratory can successfully replicate results using a specific test protocol at different times.*

Immunological: Relating to the immune system and immune responses.

In vivo: In the living organism. Refers to assays performed in multicellular organisms.

Local lymph node assay (LLNA): An *in vivo* test method used to assess the skin sensitization potential of a substance by measuring the proliferation of lymphocytes in the lymph nodes draining the ears (i.e., auricular lymph nodes) of mice, subsequent to topical exposure on the ear to the substance. The traditional LLNA measures lymphocyte proliferation by quantifying the amount of tritiated thymidine (^{3}H) incorporated into the cells of the draining lymph nodes.

Lymphocyte: A white blood cell found in the blood, lymph, and lymphoid tissues, which regulates and plays a role in acquired immunity.

Negative predictivity: The proportion of correct negative responses among substances testing negative by a test method (see *two-by-two table*). It is one indicator of test method accuracy. Negative predictivity is a function of the sensitivity of the test method and the prevalence of negatives among the substances tested.*

Non-sensitizer: A substance that does not cause skin sensitization after repeated skin contact.

Performance: The accuracy and reliability characteristics of a test method (see *accuracy*, *reliability*).*

Positive control: A substance known to induce a positive response used to demonstrate the sensitivity of the test method and to allow for an assessment of variability in the conduct of the assay over time. For most test methods, the positive-control substance is tested concurrently with the test substance and the vehicle/solvent control. However, for some *in vivo* test methods, periodic studies using a positive-control substance is considered adequate by the OECD.

Positive predictivity: The proportion of correct positive responses among substances testing positive by a test method (see *two-by-two table*). It is one indicator of test method accuracy.

The definitions in this glossary are restricted to their use with respect to the rLLNA and the traditional LLNA.

* Definition used by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM 2003).

Positive predictivity is a function of the sensitivity of the test method and the prevalence of positives among the substances tested.*

Prevalence: The proportion of positives in the population of substances tested (see *two-by-two table*).*

Protocol: The precise, step-by-step description of a test, including the listing of all necessary reagents, criteria, and procedures for the evaluation of the test data.*

Quality assurance: A management process by which adherence to laboratory testing standards, requirements, and record keeping procedures is assessed independently by individuals other than those performing the testing.*

Reduction alternative: A new or modified test method that reduces the number of animals required.*

Reference test method: The accepted *in vivo* test method used for regulatory purposes to evaluate the potential of a test substance to be hazardous to the species of interest.*

Refinement alternative: A new or modified test method that refines procedures to lessen or eliminate pain or distress in animals or enhances animal well-being.*

Relevance: The extent to which a test method correctly predicts or measures the biological effect of interest in humans or another species of interest. Relevance incorporates consideration of the *accuracy* or *concordance* of a test method.*

Reliability: A measure of the degree to which a test method can be performed reproducibly within and among laboratories over time. It is assessed by calculating intra- and interlaboratory reproducibility and intralaboratory repeatability.*

Replacement alternative: A new or modified test method that replaces animals with non-animal systems or one animal species with a phylogenetically lower one (e.g., a mammal with an invertebrate).*

Reproducibility: The consistency of individual test results obtained in a single laboratory (*intralaboratory reproducibility*) or in different laboratories (*interlaboratory reproducibility*) using the same protocol and test substances (see *intra-* and *interlaboratory reproducibility*).*

rLLNA (reduced LLNA): Also called the *cut-down LLNA*, *limit test LLNA*, or *LLNA limit dose procedure*. A variant of the traditional LLNA that employs a single high dose level of the test substance rather than multiple dose levels to determine its skin sensitization potential.

Sensitivity: The proportion of all positive substances that are classified correctly as positive in a test method. It is a measure of test method accuracy (see *two-by-two table*).*

Skin sensitizer: A substance that induces an allergic response following skin contact (U.N. 2005).

Specificity: The proportion of all negative substances that are classified correctly as negative in a test method. It is a measure of test method accuracy (see *two-by-two table*).*

Stimulation index (SI): A value calculated for the local lymph node assay to assess the skin sensitization potential of a test substance. The value is calculated as the ratio of radioactivity

---

The definitions in this glossary are restricted to their uses with respect to the rLLNA and the traditional LLNA.

* Definition used by ICCVAM (ICCVAM 2003).

incorporated into the auricular lymph nodes of a group of treated mice to the radioactivity incorporated into the corresponding lymph nodes of a group of vehicle-control mice. For the traditional LLNA and the rLLNA, an SI ≥ 3 classifies a substance as a skin sensitizer.

Test: The experimental system used; used interchangeably with *test method* and *assay*.*

Test method: A process or procedure used to obtain information on the characteristics of a substance or agent. Toxicological test methods generate information regarding the ability of a substance or agent to produce a specified biological effect under specified conditions. Used interchangeably with *test* and *assay*. See also *validated test method* and *reference test*.*

Transferability: The ability of a test method or procedure to be accurately and reliably performed in different, competent laboratories.*

Two-by-two table: The two-by-two table can be used for calculating accuracy (concordance) ([c+d]/[a+b+c+d]), negative predictivity (d/[c+d]), positive predictivity (a/[a+b]), prevalence ([a+c]/[a+b+c+d]), sensitivity (a/[a+c]), specificity (d/[b+d]), false positive rate (b/[b+d]), and false negative rate (c/[a+c]).*

		New Test Outcome		
		Positive	**Negative**	**Total**
Reference Test Outcome	Positive	a	c	a + c
	Negative	b	d	b + d
	Total	**a + b**	**c + d**	**a + b + c + d**

Validated test method: An accepted test method for which validation studies have been completed to determine the relevance and reliability of this method for a specific proposed use.*

Validation: The process by which the reliability and relevance of a procedure are established for a specific purpose.*

Vehicle control: An untreated sample containing all components of a test system, including the vehicle that is processed with the test substance-treated and other control samples to establish the baseline response for the samples treated with the test substance dissolved in the same vehicle.

Weight-of-evidence (process): The strengths and weaknesses of a collection of information are used as the basis for a conclusion that may not be evident from the individual data.

The definitions in this glossary are restricted to their use with respect to the rLLNA and the traditional LLNA.

* Definition used by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM 2003).

Annex I

ECVAM Scientific Advisory Committee Statement on the Validity of the rLLNA

[This Page Intentionally Left Blank]

EUROPEAN COMMISSION
DIRECTORATE GENERAL JRC
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

ESAC Statement on the Reduced Local Lymph Node Assay (rLLNA)

At its 26th Meeting, held on 26-27 April 2007 at the European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC)[1] unanimously endorsed the following statement:

Skin sensitisation is an important toxicological endpoint with respect to human safety.

Having reviewed the final report of the independent peer review evaluation co-ordinated by ICCVAM and NICEATM[2], the report by the EMEA[3], the pre-report of the SCCNFP[4], and evidence made available since the original submissions to ICCVAM, in March 2000 the 14th meeting of ESAC stated:

> "Following a review of the scientific report and publications on the local lymph node assay (LLNA) it is concluded that the LLNA is a scientifically validated test which can be used to assess the skin sensitisation potential of chemicals. The LLNA should be the preferred method, as it uses fewer animals and causes less pain and distress than the conventional guinea-pig methods. In some instances and for scientific reasons, the conventional methods can be used."

Since its acceptance for regulatory purposes, the LLNA has proved suitable for the purposes of satisfying a range of EU and other regulatory requirements[5].

The developers of the LLNA have now undertaken a retrospective analysis of published data obtained with the LLNA[6].

They conclude that within a tiered testing strategy in the context of REACH a "reduced" version of the LLNA (rLLNA), using only a negative control group and the equivalent of the high-dose group from the full LLNA, can be used as a screening test to distinguish between sensitisers and non-sensitisers.

ESAC established a peer review panel to evaluate if there was the potential to minimise animal use by employing the rLLNA as a screening test as part of a tiered-testing strategy for chemicals.

Mindful that with the rLLNA:

- When compared with the full LLNA the rLLNA cannot and will not result in additional false positives.
- When compared with the full LLNA the rLLNA may produce a few false negatives (3:169 in the reference document, reducing to 2:169 when negative results obtained with concentrations of <10% are considered invalid)
- The test results provided by the rLLNA do not allow the determination of the potency of a sensitising chemical.

ESAC states that the peer reviewed and published information is of a quality and nature to support the use of the rLLNA within tiered-testing strategies to reliably distinguish between chemicals that are skin sensitisers and non-sensitisers, and that animal use can be minimised providing:

EUROPEAN COMMISSION
DIRECTORATE GENERAL JRC
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

- The concentration used to evaluate sensitisation potential is the maximum consistent with solubility and the need to avoid local and other systemic adverse effects, and that this principle rather than strict adherence to the specific recommended absolute concentrations as in OECD TG 429 should be used.
- Negative test results associated with testing using concentrations of less than 10%, should undergo further evaluation.
- Positive and negative (vehicle) control groups are used, as appropriate, per OECD TG 429.
- The full LLNA should be performed when it is known that an assessment of sensitisation potency is required.

ESAC recommends that further work should be undertaken to determine if the 10% concentration threshold referenced above is optimal.

Thomas Hartung
Head of Unit
ECVAM
Institute for Health & Consumer Protection
Joint Research Centre
European Commission
Ispra

27 April 2007

1. The ESAC was established by the European Commission, and is composed of nominees from the EU Members States, industry, academia and animal welfare, together with representatives of the relevant Commission services.

   This statement was endorsed by the following members of the ESAC:

   Ms Sonja Beken (Belgium)
   Ms Dagmar Jírová (Czech Republic)
   Mr Tõnu Püssa (Estonia)
   Mr Lionel Larue (France)
   Mr Manfred Liebsch (Germany)
   Ms Annalaura Stammati (Italy)
   Mr Jan van der Valk (The Netherlands)
   Mr Constantin Mircioiu (Romania)
   Mr Albert Breier (Slovakia)
   Ms Argelia Castaño (Spain)
   Mr Patric Amcoff (Sweden)
   Mr Jon Richmond (UK)
   Mr Carl Westmoreland (COLIPA)
   Ms Vera Rogiers (ECOPA)
   Ms Nathalie Alépée (EFPIA)
   Mr Robert Combes (ESTIV)
   Mr Hasso Seibert (European Science Foundation)

   The following Commission Services and Observer Organisations were involved in the consultation process, but not in the endorsement process itself.

   Mr Thomas Hartung (ECVAM; chairman)
   Mr Jens Linge (ECVAM; ESAC secretary)
   Ms Elke Anklam (Director of IHCP)
   Ms Susanna Louhimies (DG Environment)
   Ms Barbara Mentré (DG ENTR)
   Ms Grace Patlewicz (ECB, DG JRC)
   Mr Christian Wimmer (DG Research)
   Mr Hajime Kojima (JACVAM)
   Ms Laurence Musset (OECD)
   Mr Barry Philips (Eurogroup for Animal Welfare)
   Mr William Stokes (NICEATM, USA)

2. NIH (1999). The murine local lymph node assay. The results of an independent peer review evaluation coordinated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program Center for the Evaluation of Alternative Toxicological Methods (NICEATM). NIH Publication n.99-4494.
   (http://iccvam.niehs.nih.gov/methods/immunotox/immunotox.htm)

3. EMEA (2000). Report from the ad-hoc expert meeting on testing for immunohypersensitivity (11/01/2000). European Agency for the Evaluation of Medicinal Products.

4. SCCNFP (2000). Opinion adopted by the SCCNFP during the 11 th plenary meeting, 17 February 2000. (http://ec.europa.eu/health/ph_risk/committees/sccp/docshtml/sccp_out114_en.htm)

5. A Cockshott, P Evans, CA Ryan, GF Gerberick, CJ Betts, RJ Dearman, I Kimber and DA Basketter (2006). The local lymph node assay in practice: a current regulatory perspective. Human & Experimental Toxicology **25**, 387-394.

6. I Kimber, RJ Dearman, CJ Betts, GF Gerberick, CA Ryan, PS Kern, GY Patlewicz and DA Basketter (2006.) The local lymph node assay and skin sensitisation: a cut-down screen to reduce animal requirements? Contact Dermatitis **54**, 181-185.

Annex II

Physicochemical Properties of Substances Evaluated in the rLLNA

[This Page Intentionally Left Blank]

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
(16-beta)-21-(Acetyloxy)-17-hydroxy-16-methylpregna-1,4,9(11)-triene-3,20-dione	17,21-Dihydroxy-16beta-methylpregna-1,4,9(11)-triene-3,20-dione 21-acetate	910-99-6	398.50	3.56	Solid	Pharmaceutical chemicals	GSK
(1r)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquino-line [r-(r*,r*)]-2,3-bis(benzoyloxy)-butanedioate (1:1)	–	104832-01-1	745.79	3.16	Solid	Pharmaceutical chemicals	GSK
(1R,4R)-4-Isopropenyl-1-methyl-2-methylenecyclohexane	–	–	–	–	–	–	LLNA/EC3 Validation Study
(2-Bromo-5-propoxyphenyl)(2-hydroxy-4-methoxyphenyl)-methadone	–	190965-45-8	365.23	5.26	Solid	Pharmaceutical chemicals	GSK
(2e)-2-[(2-Formyl-4-hydroxyphenyl)-methylidene]-butanedioic acid	–	773059-57-7	250.21	0.83	Solid	Pharmaceutical chemicals	GSK
(2-Oxo-1-phenyl-pyrrolidin-3-yl)(triphenyl)-phosphonium bromide	–	148776-18-5	502.40	7.51	Solid	Pharmaceutical chemicals	GSK
(2R,4S)-4-(4-Acetyl-1-piperazinyl)-n-{(1r)-1-[3,5-bis(trifluoro-methyl)phenyl]-ethyl}-2-(4-fluoro-2-methylphenyl)-n-methyl-1-piperidine-carboxamide monomethane-sulfonate	–	414910-30-8	712.73	5.63	Solid	Pharmaceutical chemicals	GSK
(2S,4S)-1-[(2s)-2-Amino-3,3-bis(4-fluorophenyl)-1-oxopropyl]-4-fluoro-2-pyrroli-dine carbonitrile	Denagliptin	483369-58-0	373.38	2.31	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
(3as,4r,5s,6s,8r,9r,9ar,10r)-6-Ethenyldeca-hydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3ah-cyclopentacyclo-octen-8-yl [[(3-exo)-8-methyl-8-azabicyclo-[3.2.1]oct-3-yl]thio]-acetate	Retapamulin	224452-66-8	517.78	5.21	Solid	Pharmaceutical chemicals	GSK
(3as,4r,5s,6s,8r,9r,9ar,10r)-6-Ethenyldeca-hydro-5-hydroxy-4,6,9,10-tetra-methyl-1-oxo-3a,9-propano-3ah-cyclopentacycloocten-8-yl hydroxyacetate	Pleuromulin	125-65-5	378.51	3.98	Solid	Pharmaceutical chemicals	GSK
(3-Endo)-8-methyl-8-azabicyclo[3.2.1]-octan-3-ol	Tropine	120-29-6	141.22	-0.39	Solid	Pharmaceutical chemicals	GSK
(3r,3as,6ar)-Hexahydrofuro-[2,3-b]furan-3-ol	–	156928-09-5	130.14	-1.19	Solid	Pharmaceutical chemicals	GSK
(3r,3as,6ar)-Hexahydrofuro-[2,3-b]furan-3-yl [(1s,2r)-3-[(1,3-benzodioxol-5-ylsulfonyl)(2-methylpropyl)-amino]-2-hydroxy-1-[[4-[(2-methyl-4-thiazolyl)methoxy]phenyl]methyl]-propyl]carbamate	Brecanavir	313682-08-5	703.84	4.32	Solid	Pharmaceutical chemicals	GSK
(3R6R)-3-(2,3-Dihydro-1h-inden-2-yl)-1-[(1r)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1s)-1-methylpropyl]-2,5-piperazinedione	–	820957-38-8	494.60	2.89	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
(3S,6R)-3-isopropyl-6-methylcyclohexene	(+)-trans-p-Menth-2-ene	5113-93-9	138.25	4.70	Liquid	–	LLNA/EC3 Validation Study
(4r,5s)-(-)-1,5-Dimethyl-4-phenyl-2-imidazolidinone	–	92841-65-1	190.25	1.38	Solid	Pharmaceutical chemicals	GSK
(4r,5s)-1,5-Dimethyl-3-(1-oxo-2-propenyl)-4-phenyl-2-imidazo-lidinone	–	139109-23-2	244.30	3.33	Solid	Pharmaceutical chemicals	GSK
(4S)-1-(tert-Butoxycarbonyl)-4-fluoro-l-prolinamide	–	426844-22-6	232.26	0.98	Solid	Pharmaceutical chemicals	GSK
(4S)-1-(tert-Butoxycarbonyl)-4-fluoro-l-proline	–	203866-13-1	233.24	1.75	Solid	Pharmaceutical chemicals	GSK
(4S,5R)-1-[(1R,2R,3S)-3-(1,3-Benzodioxol-5-yl)-1-(2-benzyloxy-4-methoxyphenyl)-1-hydroxy-6-propoxy-2-indanoyl]-3,4-dimethyl-5-phenyl-2-imidazolidinone	–	190965-47-0	740.86	9.58	Solid	Pharmaceutical chemicals	GSK
(4Z)-2-Methyl-6-methyleneoct-4-ene	–	–	–	–	–	–	LLNA/EC3 Validation Study
(5R)-5-Isopropenyl-2-methyl-1-methylene-2-cyclohexene	–	–	–	–	Liquid	–	LLNA/EC3 Validation Study
(Alpha-r)-n-alpha-dimethyl-3,5-bis(trifluoro-methyl	–	334477-60-0	409.30	3.59	Solid	Pharmaceutical chemicals	GSK
(R,S)-3-Amino-2,3,4,5-tetrahydro-n-(1-methylethyl)-2,4-dioxo-n,5-diphenyl-1h-1,5-benzodiazepine-1-acetamide	–	184944-86-3	442.52	3.21	Solid	Pharmaceutical chemicals	GSK
(s)-(-)-1-Phenylpropyl-amine	–	3789-59-1	135.21	1.93	Liquid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
(S)-2-(4-Fluoro-2-methylphenyl)4-piperidinone (s)-alpha-hydroxybenzene-acetic acid salt	–	414910-13-7	359.40	1.68	Solid	Pharmaceutical chemicals	GSK
[3aS-(3aAlpha,4beta,5alpha,6alpha,8beta,9alpha,9abeta,10S*)]-6-Ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH-cyclopentacycloocten-8-yl [(methylsulfonyl)-oxy]acetate	–	60924-38-1	456.60	4.11	Solid	Pharmaceutical chemicals	GSK
[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-boronic acid	–	591249-50-2	240.07	1.79	Solid	Pharmaceutical chemicals	GSK
[4S-[1(E),4Alpha,5alpha]]-1-[3-[2-[4-Methoxy-2-(phenylmethoxy)-benzoyl]-4-propoxyphenyl]-1-oxo-2-propenyl]-3,4-dimethyl-5-phenyl-2-imidazoli-dinone	–	190965-46-9	618.74	9.34	Solid	Pharmaceutical chemicals	GSK
1-(2',3',4',5'-Tetramethylphenyl)-3-(4'-tetrabutylphenyl)-propane-1,3-dione	–	–	336.47	5.35	–	–	Gerberick
1-(2',3',4',5'-Tetramethylphenyl)butane-1,3-dione	–	167998-73-4	221.32	3.14	–	–	Gerberick
1-(2,3-epoxypropoxy)-2,2-bis [(2,3-epoxypropoxy)methylbutane	–	–	–	–	–	–	BGIA
1-(2',5' Dimethylphenyl)butane-1,3-dione	–	56290-55-2	193.27	2.65	–	–	Gerberick
1-(2',5'-diethylphenyl)butane-1,3,-dione	–	167998-76-7	221.32	3.14	–	–	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
1-(3',4',5'-Tetramethoxyphenyl)-4-dimethylpentane-1,3-dione	–	135099-98-8	297.37	2.47	–	–	Gerberick
1-(4-Ethoxy-phenyl)-2-[4-(methyl-sulfonyl)phenyl]-ethanone	–	346413-00-1	318.40	2.46	Solid	Pharmaceutical chemicals	GSK
1-(p-methoxyphenyl)-1-penten-3-one	Powdery ketone	104-27-8	190.24	2.65	Solid	–	Gerberick
1,1,3-Trimethyl-2-formyylcyclohexa-2,4-dione	Safranal	116-26-7	150.22	2.54	Liquid	Hydrocarbons, Cyclic	Gerberick
1,1-Dimethylethyl [(1s)-1-[bis(4-fluorophenyl)-methyl]-2-[(2s,4s)-2-cyano-4-fluoro-1-pyrrolidinyl]-2-oxoethyl]carba-mate	–	483368-24-7	473.50	4.14	Solid	Pharmaceutical chemicals	GSK
1,1-Dimethylethyl [(1s)-2-[4-[(2-methyl-4-thiazolyl)methoxy]phenyl]-1-(2s)-oxiranylethyl]-carbamate	–	313680-92-1	390.51	3.32	Solid	Pharmaceutical chemicals	GSK
1,1-Dimethylethyl 3-[[[[(3s)-2,3,4,5-tetrahydro-1-[2-[(1-methylethyl)phenylamino]-2-oxoethyl]-2,4-dioxo-5-phenyl-1h-1,5-benzodiazepin-3-yl]amino]carbonyl]amino] benzoate	–	305366-94-3	661.76	6.74	Solid	Pharmaceutical chemicals	GSK
1,2,3,5,6,7-Hexahydro-2-thioxo-4h-cyclopentapyrimi-din-4-one	–	35563-27-0	168.22	0.65	Solid	Pharmaceutical chemicals	GSK
1,2-Benzisothiazolin-3-one	Proxan; Proxel active	2634-33-5	151.19	1.42	Solid	Sulfur Compounds; Heterocyclic Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
1,2-Diaminocyclohexane	cis-1,2-Cyclohexanediamine	1436-59-5	114.19	0.09	Liquid	Amines	BGIA
1,2-Dibromo-2,4-dicyanobutane	–	35691-65-7	265.93	1.91	Solid	Nitriles	Gerberick
1,3-Benzodioxazole-5-sulphonyl chloride	–	115010-10-1	220.63	0.14	Solid	Pharmaceutical chemicals	GSK
1,4-dihydroquinone	–	123-31-9	110.11	1.17	Solid	Phenols	Gerberick
1,6-Bis(2,3-epoxypropoxy)hexane	Digylidyl hexanediol; 1,6-Hexanediol diglycidyl ether	16096-31-4	230.30	0.84	Liquid	Ethers	BGIA
1-[3-(Cyclopentyl-oxy)-4-methoxy-phenyl]-4-oxocyclohexane carbonitrile	–	152630-47-2	313.40	2.23	Solid	Pharmaceutical chemicals	GSK
1-[5-[(4-Fluorophenyl)methyl]-2-furanyl]ethanone	–	280571-34-8	218.23	2.97	Solid	Pharmaceutical chemicals	GSK
12-Bromo-1-dodecanol	12-Bromolauryl alcohol	3344-77-2	265.23	3.40	Solid	Alcohols	Gerberick
12-Bromododecanoic acid	12-Bromolauric acid	73367-80-3	279.21	3.02	Solid	Lipids	Gerberick
14-Hydroxynor-morphinone	–	84116-46-1	285.30	NA	Solid	Pharmaceutical chemicals	GSK
1-Bromobutane	–	109-65-9	137.02	1.82	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromodocosane	–	6938-66-5	389.51	6.25	Solid	Hydrocarbons, Halogenated	Gerberick
1-Bromododecane	Lauryl bromide	143-15-7	249.23	3.79	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromoeicosane	–	4276-49-7	361.45	5.76	Solid	Hydrocarbons, Halogenated	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
1-Bromoheptadecane	–	3508-00-7	319.36	5.02	Solid	Hydrocarbons, Halogenated	Gerberick
1-Bromohexadecane	n-Hexadecyl bromide; Palmityl bromide; Cetyl bromide	112-82-3	305.34	4.77	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromohexane	n-Hexyl bromide	111-25-1	165.07	2.31	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromononane	–	693-58-3	207.15	3.05	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromooctadecane	–	112-89-0	333.39	5.26	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromopentadecane	n-Pentadecyl bromide	629-72-1	291.31	4.53	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromotetradecane	–	112-71-0	277.28	4.28	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromotridecane	–	765-09-3	263.26	4.03	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Bromoundecane	–	693-67-4	235.20	3.54	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Butanol	–	71-36-3	74.12	1.06	Liquid	Alcohols; Lipids	Gerberick
1-Chloro-2-dinitrobenzene	Dinitrochlorobenzene	97-00-7	202.55	-0.06	Solid	Hydrocarbon, Halogenated; Nitro Compounds; Hydrocarbons, Cyclic	NTP, Gerberick
1-Chlorohexadecane	–	4860-03-1	260.89	4.65	Liquid	Hydrocarbons, Halogenated	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
1-Chloromethylpyrene	–	1086-00-6	250.72	4.89	Solid	Hydrocarbons, Cyclic; Polycyclic Compounds	Gerberick
1-Chlorononane	n-Nonyl chloride	2473-01-0	162.70	2.93	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Chlorooctadecane	Stearyl chloride	3386-33-2	288.94	5.14	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Chlorotetradecane	Myristyl chloride	2425-54-9	232.83	4.16	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Iododecane	–	4292-19-7	296.24	3.91	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Iodohexadecane	Palmityl iodide; Hexadecyl iodide	544-77-4	352.34	4.89	Liquid/ Solid	Hydrocarbons, Halogenated	Gerberick
1-Iodohexane	–	638-45-9	212.07	2.43	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Iodononane	n-Nonyl iodide	4282-42-2	254.15	3.17	Liquid	Hydrocarbons, Halogenated	Gerberick
1-Iodooctadecane	–	629-93-6	380.39	5.39	Solid	Hydrocarbons, Halogenated	Gerberick
1-Iodotetradecane	Myristyl iodide, n-Tetradecyl iodide	19218-94-1	324.29	4.40	–	Hydrocarbons, Halogenated	Gerberick
1-Methyl-3-nitronitrosoguanidine	MNNG	70-25-7	147.09	-2.13	Solid	Amidines; Nitroso Compounds	Gerberick
1-Napthol	–	90-15-3	144.17	2.54	Solid	Hydrocarbons, Cyclic	Gerberick
1-Phenyl-1,2-propanedione	–	579-07-7	148.16	1.91	Liquid	Ketones; Heterocyclic Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
1-Phenyl-2-methylbutane-1,3-dione	–	6668-24-2	179.24	2.40	–	–	Gerberick
1-Phenyloctane-1,3-dione	–	55846-68-1	221.32	3.14	–	–	Gerberick
2-(3,4-Dimethyl-phenyl)-5-methyl-2,4-dihydropyrazol-3-one	–	18048-64-1	202.26	2.28	Solid	Pharmaceutical chemicals	GSK
2-(4-Amino-2nitro-phenylamino)-ethanol	HC Red No. 3	2871-01-4	197.19	0.12	Solid	Amines	Gerberick
2-(4-Ethoxyphenyl)-3-[4-(methyl-sulfonyl)phenyl-]pyrazolo[1,5-b]-pyridazine	GW 406381	221148-46-5	393.47	3.86	Solid	Pharmaceutical chemicals	GSK
2-(4-Oxopentyl)-1h-isoindole-1,3(2h)-dione	–	3197-25-9	231.25	1.57	Solid	Pharmaceutical chemicals	GSK
2-(4-tert-Amylcyclohexyl) acetaldehyde	QRM 2113	620159-84-4	196.33	3.28	–	–	Gerberick
2-(Benzyl)tert-butyl)amino)-1-(alpha,4-dihydroxy-m-tolyl)ethane	alpha-((Benzyl-tert-butylamino)methyl)-m-xylene-4,alpha,alpha'-triol	24085-03-8	329.44	2.51	Solid	Pharmaceutical chemicals	GSK
2,2,6,6-Tetramethyl-heptane-3,5-dione	–	1118-71-4	186.30	2.40	Liquid	Ketones	Gerberick
2,2-bis-[4-(2-hydroxy-3 methacryloxypropoxy)phenyl)]-propane	Bis-GMA	1565-94-2	512.59	4.94	Liquid	Carboxylic Acids; Phenols; Macromolecular Substances	LLNA/EC3 Validation Study
2,3,4,5-Tetrahydro-n-(1-methylethyl)-2,4-dioxo-n,5-diphenyl-3-[(phenylmethoxy)-imino]-1h-1,5-benzodiazepine-1-acetamide	–	305366-97-6	546.63	7.64	Solid	Pharmaceutical chemicals	GSK
2,3-Butanedione	Erythritol anhydride; Butadiene diepoxide	431-03-8	86.09	0.68	Liquid	Ketones	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
2,3-Dimethyl-2h-indazol-6-amine	–	444731-72-0	161.21	1.01	Solid	Pharmaceutical chemicals	GSK
2,4,6-Trichloro-1,3,5-triazine	Cyanuric chloride	108-77-0	184.41	0.78	Solid	Heterocyclic Compounds	Gerberick
2,4-Diaminophenoxyethanol HCl	–	66422-95-5	168.19	-1.28	–	Amines	LLNA/EC3 Validation Study
2,4-Dichloro-pyrimidine	–	3934-20-1	148.98	1.17	Solid	Pharmaceutical chemicals	GSK
2,4-Heptadienal	–	5910-85-0	110.16	1.80	–	Aldehydes; Hydrocarbons, Acyclic	Gerberick
2,4-Hexadienal	–	142-83-6	96.13	1.37	Liquid	Aldehydes; Hydrocarbons, Acyclic	LLNA/EC3 Validation Study
2,5-Diaminotoluene	–	95-70-5	122.08 (sulfate 156.25)	1.42	Solid (sulfate)	Amines	Gerberick
2,6-Dimethoxy-4-methyl-5-[3-(trifluoromethyl)-phenoxy]-8-quinolinamine	–	106635-86-3	378.35	5.73	Solid	Pharmaceutical chemicals	GSK
2,6-Dimethoxy-4-methyl-8-nitro-5-[3-(trifluoromethyl)-phenoxy]quinoline	–	189746-15-4	408.34	6.09	Solid	Pharmaceutical chemicals	GSK
2.4-Dinitrobenzene sulfonic acid	DNBS	89-02-1	248.17	-1.53	Liquid	Hydrocarbons, Cyclic; Sulfur Compounds	Ryan
2-[(Benzyloxy)-imino]malonic acid	–	305366-96-5	223.19	1.36	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
2-[1-(4-Bromophenyl)-1-phenylethoxy]-n,n-dimethylethanamine hydrochloride	Bromadryl	13977-28-1	384.75	4.71	Solid	Pharmaceutical chemicals	GSK
2-Acetylcyclohexanone	–	874-23-7	143.21	1.66	Solid	Hydrocarbons, Cyclic; Ketones	Gerberick
2-Amino-6-chloro-4-nitrophenol	–	6358-09-4	188.57	0.26	Solid	Amines	Gerberick
2-Amino-di-phenylamine	–	534-85-0	184.24	2.39	Solid	Pharmaceutical chemicals	GSK
2-Aminoethyl-methylsulfone	–	49773-20-8	159.63	-1.64	Solid	Pharmaceutical chemicals	GSK
2-Aminophenol	o-Aminophenol; 2-Hydroxyaniline	95-55-6	109.13	1.17	Solid	Amines; Phenols	Gerberick
2-Benzyl-tert-butylamino-3'-hydroxymethyl-4'-hydroxyaceto-phenone hydrochloride	Ethanone, 2-((1,1-dimethylethyl) (phenymethyl)amino)-1-(4-hydroxy-3-(hydroxymethyl) phenyl)-, hydrochloride	24085-08-3	363.89	3.34	Solid	Pharmaceutical chemicals	GSK
2-Bromo-5-hydroxy-benzaldehyde	–	2973-80-0	201.02	2.45	Solid	Pharmaceutical chemicals	GSK
2-Bromo-5-propoxybenzoic acid	–	190965-43-6	259.10	3.33	Solid	Pharmaceutical chemicals	GSK
2-Bromotetradecanoic acid	2-Bromomyristic acid	10520-81-7	307.27	3.51	Solid	Carboxylic Acids	Gerberick
2-Chloro-6-methoxy-4-methylquinoline	–	6340-55-2	207.66	3.57	Solid	Pharmaceutical chemicals	GSK
2-Hydroxyethyl acrylate	HEA	818-61-1	116.12	0.54	Liquid	Carboxylic Acids	Gerberick
2-Hydroxypropyl methacrylate	2-HPMA	923-26-2	144.17	1.03	Solid	Carboxylic Acids	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
2-Mercaptobenzothiazole	Captax	149-30-4	167.25	1.80	Solid	Heterocyclic Compounds	Gerberick
2-Methoxy-4-methylphenol	Cresol	93-51-6	138.16	1.66	Liquid	Phenols	Gerberick
2-Methyl-2H-isothiazol-3-one	–	2682-20-4	115.15	0.68	Solid	Sulfur Compounds; Heterocyclic Compounds	Gerberick
2-Methyl-4H,3,1-benzoxazin-4-one	Product 240	525-76-8	161.16	1.52	Solid	–	Gerberick
2-Methyl-5-hydroxyethylaminophenol	–	55302-96-0	167.21	1.32	–	–	Gerberick
2-Methylundecanal	–	110-41-8	184.32	3.03	Liquid	Aldehydes	Gerberick
2-Morpholinoethyl isocyanide	–	443882-99-3	281.67	4.55	Solid	Pharmaceutical chemicals	GSK
2-Nitro-4-(propylthio)benzen-amine	–	54393-89-4	212.27	3.45	Liquid	Pharmaceutical chemicals	GSK
2-Nitro-p-phenylenediamine	–	5307-14-2	153.13	0.01	Solid	Amines	Gerberick
3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexane-1-carboxaldehyde	Lyral	31906-04-4	210.32	2.89	Liquid	Aldehydes; Hydrocarbons, Cyclic	Gerberick
3, 3', 4', 5-Tetrachlorosalicylanilide	3,5-Dichloro-N-(3,4-dichlorophenyl)-2-hydroxybenzamide; TCS	1154-59-2	351.01	3.49	Solid	Amides; Amines	Gerberick
3,4-Dichloroaniline hydrochloride	–	95-76-1	162.02	2.60	Solid	Pharmaceutical chemicals	GSK
3,4-Dihydrocoumarin	Hydroxydihydro-cinnamic acid lactone	119-84-6	148.16	1.91	Liquid	Heterocyclic Compounds	Gerberick
3,4-epoxyclohexylethyl-cyclopolymethylsiloxane	Tet-sil	–	–	–	–	–	LLNA/EC3 Validation Study

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
3,5,5-Trimethylhexanoyl chloride	–	36727-29-4	176.68	2.54	Liquid	Carboxylic Acids	Gerberick
3-[(2r)-3-[[2-(2,3-Dihydro-1h-inden-2-yl)-1,1-dimethyl-ethyl]amino]-2-hydroxypropoxy]-4,5-difluoro-benzene propanoic acid	–	753449-67-1	447.53	2.13	Solid	Pharmaceutical chemicals	GSK
3'-[(2z)-[1-(3,4-Dimethylphenyl)-1,5-dihydro-3-methyl)-5-oxo-4h-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, compound with 2-aminoethanol (2:1)	Eltrombopag Olamine	496775-62-3	564.65	5.25	Solid	Pharmaceutical chemicals	GSK
3-[4-[(6-Bromohexyl)oxy]-butyl]benzene-sulfonamide	–	452342-04-0	392.36	3.48	Solid	Pharmaceutical chemicals	GSK
3-Aminomethyl-3,5,5-trimethylcyclohexylamine	5-Amino-1,3,3-trimethyl-cyclohexane-methylamine; IPDA; Isophorone diamine	2855-13-2	170.30	1.90	Liquid	Amines	BGIA
3-Aminophenol	m-Aminophenol; 3-Hydroxyaniline	591-27-5	109.13	1.17	Solid	Amines; Phenols	Gerberick
3-Bromomethyl-5, 5'-dimethyl-dihydro-2(3H)-furanone	–	154750-20-6	207.07	1.79	–	–	Gerberick
3-Chloro-4-fluorobenzoyl chloride	–	65055-17-6	193.01	2.42	Solid	Pharmaceutical chemicals	GSK
3-Dimethylaminopropylamine	N,N-Dimethyl-1,3-propanediamine; DMAPA	109-55-7	102.18	0.92	Liquid	Amines	Gerberick
3-Ethoxy-1-(2',3',4',5'-tetramethylphenyl)propane-1,3-dione	–	170928-69-5	248.32	3.00	–	–	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
3-Fluoro-5-(3-pyridinyl)benzen-amine	–	181633-36-3	188.21	1.80	Solid	Pharmaceutical chemicals	GSK
3-Hydroxy-2-phenyl-4-quinolinecarboxylic acid	Oxycinchophen	485-89-2	265.27	4.95	Solid	Pharmaceutical chemicals	GSK
3-Hydroxy-4-methoxybenzaldehyde	Isovanillin	621-59-0	152.15	1.28	Solid	Pharmaceutical chemicals	GSK
3-Methyl-4-phenyl-1,2,5-thiadiazole-1,1-dioxide	MPT	3775-21-1	208.24	1.14	–	–	Gerberick
3-Methyleugenol	–	186743-26-0	178.23	2.40	–	Ethers; Phenols	Gerberick
3-Methylisoeugenol	–	186743-29-3	178.23	2.40	–	Carboxylic Acids	Gerberick
3-Phenylenediamine	m-Phenylenediamine	108-45-2	108.14	1.17	Solid	Amines	Gerberick
3-Propoxybenzoic acid	–	190965-42-5	180.21	3.08	Solid	Pharmaceutical chemicals	GSK
3-Propylidenphthalide	–	17369-59-4	174.20	2.40	Liquid	–	Gerberick
4-(Bromomethyl)-benzoic acid ethyl ester	–	26496-94-6	243.10	3.42	–	Pharmaceutical chemicals	GSK
4-(N-Ethyl-N-2-methan-sulfamido-ethyl)-2-methyl-1,4,-phenylenediamine	CD-4 developer	25646-71-3	836.97	-2.12	Solid	Amides; Sulfur Compounds	Gerberick
4'-(Trifluoro-methyl)-[1,1'-biphenyl]-4-carboxaldehyde	–	90035-34-0	250.22	4.31	Solid	Pharmaceutical chemicals	GSK
4,4,4-Trifluoro-1-phenylbutane-1,3-dione	BFA	362-06-7	219.18	2.52	–	–	Gerberick
4,4-Dibromobenzil	–	35578-47-3	368.02	5.34	Solid	–	LLNA/EC3 Validation Study

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
4-[4-[[(3R)-1-Butyl-3-[(r)-cyclohexyl-hydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]-undec-9-yl]methyl]phenoxy]benzoic acid	Aplaviroc	461443-59-4	577.73	3.92	Solid	Pharmaceutical chemicals	GSK
4-Allylanisole	Estragole	140-67-0	148.20	2.54	Liquid	Ethers; Phenols	Gerberick
4-Amino-3-nitrophenyl thiocyanate	–	54029-45-7	195.20	2.21	Solid	Pharmaceutical chemicals	GSK
4-Bromo-1-phthalimidopentane	–	59353-62-7	296.17	3.48	Liquid	Pharmaceutical chemicals	GSK
4-Chloro-6-iodoquinazoline	–	98556-31-1	290.49	2.96	Solid	Pharmaceutical chemicals	GSK
4-Fluoro-2-pyrrolidine-carboxamide	–	748165-40-4	132.14	-1.01	Solid	Pharmaceutical chemicals	GSK
4-Hydroxybenzoic acid	–	99-96-7	138.12	1.03	Solid	Phenols; Carboxylic Acids	Gerberick
4-Iodo-1-phthalimido-pentane	–	63460-47-9	343.17	3.87	Solid	Pharmaceutical chemicals	GSK
4-Isopropyl-1-methylenecyclohexane	–	–	–	–	–	–	LLNA/EC3 Validation Study
4'-Methoxyacetophenone	–	100-06-1	150.18	1.91	Solid	Ethers	Gerberick
4-Methylaminophenol sulfate	Metol; Paramethyl-aminophenol sulfate	55-55-0	344.38	-0.13	Solid	Amines; Phenols	Gerberick
4-Nitrobenzyl bromide	1-(Bromomethyl)-4-nitrobenzene	100-11-8	216.03	1.40	Solid	Hydrocarbons, Cyclic; Nitro Compounds	Gerberick
4-Phenylenediamine	p-PDA, p-Phenylenediamine	106-50-3	108.14	1.17	Solid	Amines	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
5,5-Dimethyl-3-methylenedihydro-2(3H)-furanone	–	29043-97-8	126.16	1.42	–	Heterocyclic Compounds; Sulfur Compounds; Lactones	Gerberick
5-[[4-[(2,3-Dimethyl-2h-indazol-6-yl)-methylamino]-2-pyrimidinyl]amino]-2-methylbenzene-sulfonamide	Pazopanib	444731-52-6	437.53	3.65	Solid	Pharmaceutical chemicals	GSK
5-Amino-2-methylbenzene-sulfonamide	–	69733-09-7	186.23	-0.07	Solid	Pharmaceutical chemicals	GSK
5-Amino-O-Cresol	2-Hydroxy-p-toluidine	2835-95-2	123.15	0.79	Solid	–	NTP
5-Chloro-2,6-dimethoxy-4-methyl-8-nitroquinoline	–	189746-21-2	282.69	3.95	Solid	Pharmaceutical chemicals	GSK
5-Chloro-2,6-dimethoxy-4-methylquinoline	–	189746-19-8	237.69	4.13	Solid	Pharmaceutical chemicals	GSK
5'-Chloro-2'-hydroxy-3'-nitro-[1,1'-biphenyl]-3-carboxylic acid	–	376592-58-4	293.67	4.03	Solid	Pharmaceutical chemicals	GSK
5-Chloro-2-methyl-4-isothiazolin-3-one	–	26172-55-4	149.60	0.92	Liquid	Sulfur Compounds; Heterocyclic Compounds	Gerberick
5-Chloro-6-methoxy-4-methyl-8-nitro-2(1h)quinolinone	–	189746-23-4	268.66	1.99	Solid	Pharmaceutical chemicals	GSK
5-Methoxy-2-nitro-4-(trifluoromethyl)benzene acetonitrile	–	178896-77-0	260.17	2.42	Solid	Pharmaceutical chemicals	GSK
5-Methoxy-6-(trifluoromethyl)-2,3-dihydro-1h-indole	–	178896-79-2	217.19	3.25	Solid	Pharmaceutical chemicals	GSK
5-Methyl-2,3-hexanedione	Acetyl isovaleryl	13706-86-0	128.17	1.42	Liquid	–	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
5-Methyl-2-phenyl-2-hexenal	–	21834-92-4	188.27	3.77	Liquid	–	LLNA/EC3 Validation Study
5-Methyleugenol	–	186743-25-9	178.23	2.40	–	Ethers; Phenols	Gerberick
6-(Diethylamino)-1-hexanol	–	06947-12-2	173.30	1.73	Liquid	Pharmaceutical chemicals	GSK
6-(Trifluoro-methyl)-2,3-dihydro-5-methyl-1h-indole, hydrochloride	–	280121-24-6	237.65	3.69	Solid	Pharmaceutical chemicals	GSK
6-[(2-Methyl-3-pyridinyl)oxy]-3-pyridinamine	–	181633-42-1	201.23	1.42	Solid	Pharmaceutical chemicals	GSK
6-Chloro-1-hexanol	–	2009-83-8	136.62	1.59	Liquid	Pharmaceutical chemicals	GSK
6-Diethylaminohexyl bromide hydrobromide	–	64993-14-2	317.11	3.57	Solid	Pharmaceutical chemicals	GSK
6-Iodo-quinazolin-4-ol	–	16064-08-7	272.05	1.49	Solid	Pharmaceutical chemicals	GSK
6-Methoxy-4-methyl-2(1H)-quinolinone	–	5342-23-4	189.22	1.51	Solid	Pharmaceutical chemicals	GSK
6-Methylcoumarin	6-MC	92-48-8	160.17	2.15	Solid	Heterocyclic Compounds	Gerberick
6-Methyleugenol	–	186743-24-8	178.23	2.40	–	Ethers; Phenols	Gerberick
6-Methylisoeugenol	–	13041-12-8	178.23	2.40	–	Carboxylic Acids	Gerberick
7,12-Dimethylbenz[a]anthracene	DMBA; 9,10-Dimethyl-1,2-benzanthracene	57-97-6	256.34	5.39	Solid	Hydrocarbons, Cyclic; Polycyclic Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow} [1,2]	Physical Form	Chemical Class[3]	Data Source
7-[(4z)-3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethane-sulfonate	Gemifloxacin mesylate	210353-53-0	485.50	-1.25	Solid	Pharmaceutical chemicals	GSK
7-Bromotetradecane	7-Tetradecyl bromide; 7-Myristyl bromide	74036-97-8	277.29	4.28	–	Hydrocarbons, Halogenated	Gerberick
8-[(4-Phthalimido-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy) quinoline	–	106635-87-4	593.61	8.70	Solid	Pharmaceutical chemicals	GSK
8-Amino-6-methoxy-4-methylquinoline	–	57514-21-3	188.23	2.30	Solid	Pharmaceutical chemicals	GSK
8-Chloro-3-pentyl-3,7-dihydro-1h-purine-2,6-dione	–	862892-90-8	256.69	2.27	Solid	Pharmaceutical chemicals	GSK
8-Hydroxy-5-[(1r)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]-ethyl]amino]ethyl]-2(1h)-quinolinone	–	530084-87-8	521.62	3.98	Solid	Pharmaceutical chemicals	GSK
A SC600	–	–	–	–	–	Formulation	Bayer
Abietic acid	Sylvic acid	514-10-3	302.46	4.61	Solid	Hydrocarbons, Cyclic; Polycyclic Compounds	Gerberick
Adipic acid	1,4-Butanedicarboxylic acid	124-04-9	146.14	-0.02	Solid	Pharmaceutical chemicals	GSK
AE F016382 00 TK71 A101	–	–	–	–	–	Formulation	Bayer

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Alpha-(p-toluenesulfonyl)-4-fluorobenzyliso-nitrile	–	165806-95-1	289.33	2.04	Solid	Pharmaceutical chemicals	GSK
alpha-Amyl cinnamic aldehyde	–	122-40-7	202.30	3.52	Solid	Aldehydes	Gerberick
alpha-Butyl cinnamic aldehyde	–	7492-44-6	188.27	3.28	Liquid	Aldehydes	Gerberick
alpha-Methyl cinnamic aldehyde	–	101-39-3	146.19	2.54	Liquid	Aldehydes	Gerberick
alpha-Methylphenylacetaldehyde	2-Phenyl propionaldehyde	93-53-8	134.18	2.29	Liquid	Aldehydes	Gerberick
alpha-Phellandrene	Menthadiene; Dihydro-p-cymene; p-Mentha-1,5-diene; 2-methyl-5-(1-methylethyl)- 1,3-cyclohexadiene	99-83-2	136.23	4.62	Solid	Hydrocarbons, Cyclic; Hydrocarbons, Other	LLNA/EC3 Validation Study
alpha-Terpinene	1-Isopropyl-4-methyl-1,3-cyclohexadiene; p-Mentha-1,3-diene	99-86-5	136.23	4.75	Solid	Hydrocarbons, Other	LLNA/EC3 Validation Study
Aniline	Benzenamine	62-53-3	93.13	1.56	Liquid	Amines	Gerberick
Anthranilic acid	–	118-92-3	131.14	1.21	Solid	Pharmaceutical chemicals	GSK
Atrazine SC	–	1912-24-9	215.68	2.82	Solid	Heterocyclic Compounds	ECPA, NTP
Azithromycin	–	83905-01-5	748.99	3.24	Solid	Polycyclic Compounds; Carbohydrates, Lactones	NTP
Bakelite EPR 161	–	9012-45-7	–	–	Solid	Macromolecular substances	BGIA
Bakelite EPR 162	–	9012-45-7	–	–	Solid	Macromolecular substances	BGIA

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Bakelite EPR 164	–	9012-45-7	–	–	Solid	Macromolecular substances	BGIA
Bandrowski's base	1,4-Cyclohexadiene-1,4-diamine; 1,4-Benzenediamine; N,N''-(2,5-diamino-2,5-cyclohexadiene-1,4-diylidene)bis-(9CI)	20048-27-5	318.38	0.74	Solid	Amines	LLNA/EC3 Validation Study
Basil oil	Ocimum basilicum herb oil	8015-73-4	–	–	Liquid	Lipids	Lalko & Api
Benzaldehyde	–	100-52-7	106.12	1.80	Liquid	Aldehydes	Gerberick
Benzalkonium chloride	–	8001-54-5	–	–	–	Onium Compounds	CESIO
Benzene-1,3,4-tricarboxylic anhydride	Trimellitic anhydride	552-30-7	192.13	0.75	Solid	Anhydrides; Carboxylic Acids	Gerberick
Benzo[a]pyrene	–	50-32-8	252.31	5.39	Solid	Hydrocarbons, Cyclic; Polycyclic Compounds	Gerberick
Benzocaine	–	94-09-7	165.19	1.52	Solid	Carboxylic Acids	Gerberick
Benzoquinone	p-Quinone; 1,4-Cyclohexadienedione	106-51-4	108.10	1.17	Solid	Quinones	Gerberick
Benzyl benzoate	–	120-51-4	212.25	3.14	Liquid	Carboxylic Acids	Gerberick
Benzyl bromide	alpha-Bromotoluene	100-39-0	171.03	2.56	Liquid	Hydrocarbons, Cyclic	Gerberick
Benzylidene acetone	4-phenyl-3-buten-2-one	122-57-6	146.19	2.54	Solid	Ketones	Gerberick
beta-Phellandrene	3-methylene-6-(1-methylethyl) cyclohexene; p-Mentha-1(7),2-diene	555-10-2	136.23	4.70	–	Hydrocarbons, Cyclic; Hydrocarbons, Other	LLNA/EC3 Validation Study

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
beta-Phenylcinnamaldehyde	–	1210-39-5	208.23	2.78	Liquid	–	LLNA/EC3 Validation Study
beta-Propiolactone	–	57-57-8	72.06	0.43	Liquid	Lactones	Gerberick
beta-Terpinene	p-Mentha-1(7),3-diene; (1-methylethyl)-4-methylene-1-cyclohexene	99-84-3	136.23	4.83	–	Hydrocarbons, Other	LLNA/EC3 Validation Study
bis-1,3-(2',5'-dimethylphenyl)-propane-1,3-dione	–	–	282.38	4.37	–	–	Gerberick
Bis-3,4-epoxycyclohexyl-ethyl-phenyl-methylsilane	Ph-Sil	–	–	–	–	–	LLNA/EC3 Validation Study
Bisphenol A-diglycidyl ether	–	1675-54-3	340.42	4.09	Liquid	Ethers	Gerberick
Butyl acrylate	n-butyl acrylate; n-Butyl propenoate; 2-Propenoic acid; Butyl ester	141-32-2	128.17	2.20	Liquid	Carboxylic Acids	NTP, LLNA/EC3 Validation Study
Butyl glycidyl ether	–	2426-08-6	130.19	1.42	Liquid	Ethers	Gerberick
C11-azlactone	–	176665-06-8	267.41	3.24	–	–	Gerberick
C15-azlactone	–	176665-09-1	323.52	4.23	–	–	Gerberick
C17-azlactone	–	176665-11-5	351.58	4.72	–	–	Gerberick
C19-azlactone	–	–	379.63	5.21	–	–	Gerberick
C4-azlactone	–	176664-99-6	169.22	1.52	–	–	Gerberick
C6-azlactone	–	176665-02-4	197.28	2.01	–	–	Gerberick
C9-azlactone	–	176665-04-6	239.36	2.75	–	–	Gerberick
Camphorquinone	Camphoroquinone	465-29-2	166.22	2.15	Solid	Hydrocarbons, Other	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Chlorobenzene	–	108-90-7	112.56	2.19	Liquid	Hydrocarbons, Cyclic; Hydrocarbons, Halogenated	Gerberick
Chlorothalonil	Tetrachloroiso-phthalodinitrile	1897-45-6	265.91	3.66	Solid	Nitriles	LLNA/EC3 Validation Study
Cinnamic alcohol	–	104-54-1	134.18	2.29	Solid	Alcohols	Gerberick
Cinnamic aldehyde	Cinnamaldehyde	104-55-2	132.16	2.29	Liquid	Aldehydes	Gerberick
cis-4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclo-hexanecarboxylic acid	Cilomilast	153259-65-5	343.23	3.20	Solid	Pharmaceutical chemicals	GSK
cis-6-Nonenal	–	2277-19-2	140.23	2.29	Liquid	Aldehydes	Gerberick
Citral	3,7-Dimethyl-2,6-octadienal; Geranial-Neral mixture	5392-40-5	152.23	2.54/ 3.45	Liquid	Hydrocarbons, Other	Lalko & Api, Gerberick
Citronella oil	–	8000-29-1	–	–	Liquid	Lipids	Lalko & Api
Clarithromycin	–	81103-11-9	747.95	3.18	Solid	Polycyclic Compounds; Carbohydrates; Lactones	NTP
Clotrimazole	–	23593-75-1	344.84	5.35	Solid	Heterocyclic Compounds	Gerberick
Clove bud oil	Clove oil; Oil of cloves	8000-34-8	–	–	Liquid	Lipids	Lalko & Api
Clove leaf oil	–	8015-97-2	–	–	Liquid	Lipids	Lalko & Api
Clove stem oil	–	8015-98-3	–	–	Liquid	Lipids	Lalko & Api
Coumarin	–	91-64-5	146.15	1.91	Solid	Heterocyclic Compounds	Gerberick
Cyclamen aldehyde	–	103-95-7	190.29	3.28	Liquid	Carboxylic Acids	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Cytosine	4-Amino-2(1H)-pyrimidinone	71-30-7	120.11	-1.85	Solid	Pharmaceutical chemicals	GSK
D EC25®	–	–	–	–	–	Formulation	Bayer
D EW 15	–	–	–	–	–	Formulation	Bayer
Dicyclohexylcarbodiimide	–	538-75-0	206.33	6.83	Solid	Imines	NTP
Diethyl maleate	–	141-05-9	172.18	0.89	Liquid	Carboxylic Acids	Gerberick
Diethyl sulfate	–	64-67-5	154.19	-0.09	Liquid	Sulfur Compounds	Gerberick
Diethylacetaldehyde	–	97-96-1	100.16	1.56	Liquid	Aldehydes	Gerberick
Diethylenetriamine	–	111-40-0	103.17	0.29	Liquid	Amines	Gerberick
Diethylpthalate	–	84-66-2	222.24	1.87	Liquid	Carboxylic Acids	Gerberick
Dihydroeugenol	2-Methoxy-4-propylphenol; 4-Propylguaicol	2785-87-7	166.22	2.15	Liquid	Ethers; Phenols	Gerberick
Dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-pimelate	–	152630-48-3	403.48	3.31	Solid	Pharmaceutical chemicals	GSK
Dimethyl carbonate	–	616-38-6	90.08	0.10	Liquid	Pharmaceutical chemicals	GSK
Dimethyl sulfate	–	77-78-1	126.13	-0.59	Liquid	Sulfur Compounds	Gerberick
Dimethylsulfoxide	–	67-68-5	78.13	0.57	Liquid	Sulfur Compounds	Gerberick
Dinocap EC	–	39300-45-3	364.39	5.76	Liquid	Hydrocarbons, Cyclic	ECPA
Dipropylene triamine	Bis(3-aminopropyl)amine	56-18-8	131.22	-1.15	Liquid	Amines	BGIA
Dodecyl methanesulfonate	Lauryl methanesulfonate	51323-71-8	264.43	2.51	–	Esters; Sulfur Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Endo-tropine-3-mesylate	–	35130-97-3	219.31	-0.11	Solid	Pharmaceutical chemicals	GSK
Ethyl (3-endo)-8-methyl-8-azabicyclo[3.2.1]-octane-3-acetate	–	56880-11-6	211.31	1.53	Liquid	Pharmaceutical chemicals	GSK
Ethyl (z)-alpha-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]-2-[(triphenylmethyl)amino]- 4-thiazoleacetate	–	68672-65-1	599.76	7.75	Solid	Pharmaceutical chemicals	GSK
Ethyl 1h-1,2,4-triazole-3-carboxylate	–	64922-04-9	141.13	-0.02	Solid	Pharmaceutical chemicals	GSK
Ethyl 2,6-dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	–	96568-04-6	280.09	2.15	Solid	Pharmaceutical chemicals	GSK
Ethyl 4-iodobenzoate	–	51934-41-9	276.08	3.76	Liquid	Pharmaceutical chemicals	GSK
Ethyl benzoylacetate	–	94-02-0	192.21	2.01	Liquid	Esters; Ethers	Gerberick
Ethyl vanillin	–	121-32-4	166.18	1.52	Solid	Aldehydes	Gerberick
Ethyl-2-(Hydroxymethyl)-1,3-Propanediol Triacrylate	–	–	–	–	–	–	NTP
Ethylacrylate	–	140-88-5	100.12	0.92/ 1.22	Liquid	Carboxylic Acids	NTP, Gerberick
Ethylene glycol dimethacrylate	EGDMA	97-90-5	198.22	1.38	Liquid	Carboxylic Acids	Gerberick
Ethylenediamine free base	–	107-15-3	60.10	0.19	Liquid	Amines	Gerberick
Ethylhexyl acrylate	Octyl acrylate; 2-Ethylhexyl 2-propenoate; Acrylic acid; 2-ethylhexyl ester	103-11-7	184.28	4.09	Liquid	Carboxylic Acids	LLNA/EC3 Validation Study

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Eugenol	2-Methoxy-4-(2-propenyl)phenol; 4-Allyl-2-methoxyphenol; 4-Allylguaiacol	97-53-0	164.20	2.15/ 2.73	Liquid	Carboxylic Acids	Lalko & Api, Gerberick
EXP 10810 A	–	–	–	–	–	Formulation	Bayer
EXP 11120 A	–	–	–	–	–	Formulation	Bayer
F & Fo WG 50 + 25	–	–	–	–	–	Formulation	Bayer
FAR01042-00	–	–	–	–	–	Formulation	Bayer
FAR01060-00	–	–	–	–	–	Formulation	Bayer
Farnesal	–	502-67-0	220.36	3.77	Liquid	Alcohols; Hydrocarbons, other; Lipids	Gerberick
Fatty acid glutamate	–	–	–	–	–	–	CESIO
Fluorescein isothiocyanate	FITC	27072-45-3	389.38	3.32	Solid	Polycyclic Compounds; Isocyanates; Sulfur Compounds	Gerberick
Formaldehyde	–	50-00-0	30.03	0.33/ 0.35	Liquid	Aldehydes	Ryan, Gerberick
Fumaric acid	2-Butenedioic acid; Butenedioic acid; Fumarate	110-17-8	116.07	0.05	Solid	Carboxylic Acids	EFfCI
Furil	–	492-94-4	190.15	1.38	Solid	Heterocyclic Compounds	Gerberick
Fx + Me EW 69	–	–	–	–	–	Formulation	Bayer
Geraniol	Rhodinol	106-24-1	154.25	2.54/ 3.47	Liquid	Hydrocarbons, Other	Lalko & Api, Gerberick
Geranium oil	Pelargonium oil	8000-46-2	–	–	Liquid	–	Lalko & Api
Glutaraldehyde	–	111-30-8	100.12	0.92	Liquid	Aldehydes	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Glycerol	–	56-81-5	92.09	0.05	Liquid	Alcohols; Carbohydrates	Gerberick
Glyceryl thioglycolate	Acetic acid, mercapto-, monoester with 1,2,3-propanetriol	30618-84-9	166.19	-1.29	–	Lipids	CESIO
Glyoxal	Oxaldehyde; Ethanedial; Biformyl	107-22-2	58.04	0.19	Liquid	Aldehydes	Gerberick
Hexane	–	110-54-3	86.18	1.94	Liquid	Hydrocarbons, Acyclic	Gerberick
Hexyl cinnamic aldehyde	HCA; alpha-Hexyl-cinnamaldehyde; 2-(Phenylmethylene) octanal	101-86-0	216.32	3.77/ 4.82	Liquid	Aldehydes	BGIA, Gerberick
Hydroxycitronellal	–	107-75-5	172.26	2.15	Liquid	Hydrocarbons, Other	Gerberick
Hydroxyethylethylenediamine	N-(2-Hydroxyethyl) ethylenediamine	111-41-1	104.15	-2.13	Liquid	Alcohols; Amines	BGIA
Imidazolidinyl urea	Germall 115, Imidurea	39236-46-9	388.29	-3.00	Solid	Urea	Gerberick
Iodopropynyl butylcarbamate	3-iodo-2-propynylbutyl-carbamate	87977-28-4	281.09	2.45	Solid	Carboxylic Acids	LLNA/EC3 Validation Study
Isoeugenol	2-Methoxy-4-propenylphenol; 4-Propenylguaiacol	97-54-1	164.20	2.15	Liquid	Carboxylic Acids	Gerberick
Isononanoyl chloride	–	57077-36-8	176.69	2.54	–	Carboxylic Acids	Gerberick
Isopropanol	Isopropyl alcohol, 2-Propanol	67-63-0	60.10	0.82	Liquid	Alcohols	Gerberick
Isopropyl dicyandiamide	–	35695-36-4	126.16	0.51	Solid	Pharmaceutical chemicals	GSK
Isopropyl myristate	–	110-27-0	270.46	3.88	Liquid	Lipids	Gerberick
Isopropyleugenol	–	51474-90-9	206.29	2.89	–	Ethers; Phenols	Gerberick
Isopropylisoeugenol	–	2953-00-7	206.29	2.89	–	Ethers	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Jasmine absolute (Grandiflorum)	Jasmine oil	8022-96-6	–	–	Liquid	Lipids	Lalko & Api
Jasmine absolute (Sambac)	Jasmine oil	8022-96-6	–	–	Liquid	Lipids	Lalko & Api
Kanamycin	–	59-01-8; 8063-07-8	484.50	-0.90	Solid	Carbohydrates	Gerberick
Lactic acid	2-Hydroxypropanoic acid	598-82-3	90.08	0.05	Liquid	Carboxylic Acids	Gerberick
Lauryl gallate	–	1166-52-5	338.44	3.21	Solid	Carboxylic Acids	Gerberick
Laurylglycerin derivitive	–	–	–	–	–	–	CESIO
Lemongrass oil	Citral terpenes; Indian melissa oil; Indian oil of verbena; Cymbopogon citratus oil	8007-02-1	–	–	Liquid	Lipids; Hydrocarbons, other	Lalko & Api
Linalool alcohol	Linalool; Linalol; Linalyl alcohol	78-70-6	154.25	2.54/ 3.38	Liquid	Hydrocarbons	Gerberick, LLNA/EC3 Validation Study
Linalool aldehyde	–	–	–	–	–	–	LLNA/EC3 Validation Study
Linoleic acid	Grape seed oil	60-33-3	280.45	7.51	Liquid	Lipids	EFfCI
Linolenic acid	9,12,15-Octadecatrienoic acid	463-40-1	278.43	7.30	Liquid	Lipids	EFfCI
Litsea cubeba oil	–	68855-99-2	–	–	Liquid	–	Lalko & Api
Maleic acid	cis-Butenedioic acid; Toxilic acid	110-16-7	116.07	0.05	Solid	Carboxylic Acids	EFfCI
m-Chloropropio-phenone	3'-Chloropropiophenone	34841-35-5	168.62	2.90	Solid	Pharmaceutical chemicals	GSK
Methyl 4-(bromomethyl)benzoate	–	2417-72-3	229.08	2.89	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Methyl 4-(bromomethyl)benzoate	–	2417-72-3	229.08	2.89	Solid	Pharmaceutical chemicals	GSK
Methyl acrylate	Methyl propenoate; Acrylic acid methyl ester; Methoxy-carbonylethylene	96-33-3	86.09	0.73	Liquid	Carboxylic Acids	LLNA/EC3 Validation Study
Methyl dodecanesulfonate	–	2374-65-4	264.43	2.51	–	Esters; Sulfur Compounds	Gerberick
Methyl hexacecyl sulfonate	–	4230-15-3	320.53	3.49	–	Hydrocarbons, Acyclic; Sulfur Compounds	Gerberick
Methyl hexadecenesulfonate	–	26452-48-2	318.52	3.49	–	Ethers; Sulfur Compounds	Gerberick
Methyl methanesulfonate	–	66-27-3	110.13	-0.20	Liquid	Hydrocarbons, Acyclic; Sulfur Compounds	Gerberick
Methyl pyruvate	–	600-22-6	102.09	-0.96	Liquid	Carboxylic Acids	LLNA/EC3 Validation Study
Methyl salicylate	Oil of wintergreen, 2-Hydroxybenzoic acid methyl ester	119-36-8	152.15	1.28/2.60	Liquid	Phenols; Carboxylic Acids	NTP, Gerberick
Methyl(2-sulfomethyl) octadecanoate	–	–	454.67	4.89	–	Ethers; Sulfur Compounds	Gerberick
Methyl-2-nonynoate	–	111-80-8	168.24	2.15	Liquid	Lipids	Gerberick
Methyl-4-hydroxybenzoate	Methylparaben	99-76-3	152.15	1.28	Solid	Carboxylic Acids	Gerberick
Methylmethacrylate	Pegalan	80-62-6	100.12	1.28	Liquid	Carboxylic Acids; Macromolecular Substances	LLNA/EC3 Validation Study

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
m-Phenylenebis(methylamine)	1,3-xylenediamine; m-Xylylenediamine; 1,3-Bis(aminomethyl)-benzene	1477-55-0	136.19	0.15	Liquid	Hydrocarbons, Cyclic	BGIA
n-(2-Chloro-4-pyrimidinyl)-2,3-drimethyl-2h-indazol-6-amine	–	444731-74-2	273.73	3.02	Solid	Pharmaceutical chemicals	GSK
n-(2-Chloro-4-pyrimidinyl)-n,2,3-trimethyl-2h-indazol-6-amine	–	444731-75-3	287.75	2.88	Solid	Pharmaceutical chemicals	GSK
n-(3,4-Dichlorophenyl)-n'-(1-methylethyl)-imidodicarbonimidic diamide monohydrochloride	Chlorproguanil hydrochloride	15537-76-5	324.64	3.22	Solid	Pharmaceutical chemicals	GSK
n-(4-Methoxyphenyl)-3-oxobutanamide	–	5437-98-9	207.23	0.88	Solid	Pharmaceutical chemicals	GSK
n-[(1,1-Dimethylethoxy)-carbonyl]-l-tyrosine, ethyl ester	–	72594-77-5	309.37	2.66	Solid	Pharmaceutical chemicals	GSK
n-[(1-Butyl-4-piperidinyl)methyl]-3,4-dihydro-2h-[1,3]oxazino[3,2-a]indole-10-carboxamide	Piboserod	152811-62-6	369.51	4.01	Solid	Pharmaceutical chemicals	GSK
n-[2-(Diethylamino)ethyl]-2-[[(4-fluorophenyl)-methyl]thio]-4,5,6,7-tetrahydro-4-oxo-n-[[4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]-1h-cyclopentapyrim-idine-1-acetamide	–	356057-34-6	666.79	8.33	Solid	Pharmaceutical chemicals	GSK
n-[2-Benzyloxy-5-(2-bromo-1-hydroxy-ethyl)-phenyl]-formamide	–	201677-59-0	350.22	2.51	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
n-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-fluoro-beta-(4-fluorophenyl)-l-phenylalanine	–	481055-29-2	377.39	4.31	Solid	Pharmaceutical chemicals	GSK
n-Amino-pyridinium	–	35073-04-2	223.02	0.35	Solid	Pharmaceutical chemicals	GSK
N-Ethyl-N-nitrosourea	ENU	759-73-9	117.11	-0.73	Solid	Nitroso Compounds; Urea	Gerberick
Nickel Sulfate	–	7786-81-4	154.76	-0.17	–	Inorganic Chemical, Metals; Inorganic Chemical, Elements	Ryan
n-Isopropyl-n-phenyl-2-(2-phenylamino-phenylamino)-acetamide	–	161455-90-9	359.48	4.91	Solid	Pharmaceutical chemicals	GSK
N-Methyl-N-nitrosourea	MNU	684-93-5	103.08	-0.97	Solid	Nitroso Compounds; Urea	Gerberick
Nonanoyl chloride	Pelargonoyl chloride	764-85-2	176.68	2.54	Liquid	Carboxylic Acids	Gerberick
Non-ionic surfactant 1	–	–	–	–	–	–	CESIO
Non-ionic surfactant 2	–	–	–	–	–	–	CESIO
Non-ionic surfactant 3	–	–	–	–	–	–	CESIO
Non-ionic surfactant 4	–	–	–	–	–	–	CESIO
Non-ionic surfactant 5	–	–	–	–	–	–	CESIO
Non-ionic surfactant 6	–	–	–	–	–	–	CESIO
Non-ionic surfactant 7	–	–	–	–	–	–	CESIO
Non-ionic surfactant 8	–	–	–	–	–	–	CESIO
Non-ionic surfactant 9	–	–	–	–	–	–	CESIO

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Norbornene fluoroalcohol	2[(bicyclo[2.2.1]hept-5-ene-2-yloxy)methyl]-1,1,1,3,3,3-hexafluoro-2-propanol	305815-63-8	290.20		Liquid	–	LLNA/EC3 Validation Study
Octanoic acid	–	124-07-2	144.21	1.66	Liquid	Carboxylic Acids; Lipids	Gerberick
Octinol	Capryl alcohol; Octyl alcohol	111-87-5	130.23	2.81	Liquid	Alcohols; Lipids	EFfCI
Oleic acid	cis-9-Octadecenoic acid; Elainic acid	112-80-1	282.46	7.73	Liquid	Lipids	EFfCI
Oleyl methane sulfonate	–	35709-09-2	346.57	3.98	Liquid	Hydrocarbons, Acyclic; Sulfur Compounds	Gerberick
Oripavine	Oripavine	467-04-9	297.36	1.21	Solid	Pharmaceutical chemicals	GSK
Oxalic acid	–	144-62-7	90.03	-0.59	Solid	Carboxylic Acids	Gerberick
Oxazolone	4-Ethoxymethylene-2-phenyloxazol-5-one	15646-46-5	217.22	1.87	Solid	Heterocyclic Compounds	Gerberick
Oxirane, mono((C12-14-alkyloxy)methyl) derivs	–	68609-97-2	–	–	Liquid	–	BGIA
Oxyfluorfen EC	–	42874-03-3	361.70	5.21	Solid	Ethers	ECPA
Palmarosa oil	Cymbopogon martini oil; Geranium oil, east indian	8014-19-5	–	–	Liquid	–	Lalko & Api
Palmitoyl chloride	–	112-67-4	274.88	4.26	Liquid	Lipids	Gerberick
Penicillin G	–	61-33-6	334.39	2.09	Solid	Amides; Sulfur Compounds; Heterocyclic Compounds	Gerberick
Pentachlorophenol	Penta; PCP	87-86-5	266.34	2.79	Solid	Phenols	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Pentaerythritol Triacrylate	–	3524-68-3	298.29	0.91	–	Carboxylic Acids, Alcohols	NTP
Perillaldehyde	–	2111-75-3	150.22	2.54	Liquid	Hydrocarbons, Other	Gerberick
Phenyl benzoate	–	93-99-2	198.22	2.89	Solid	Carboxylic Acids	Gerberick
Phenylacetaldehyde	–	127-78-1	120.15	2.05	Liquid	Aldehydes	Gerberick
Phenylmethyl 2-(4-fluoro-2-methylphenyl)-4-oxo-3,4-dihydro-1(2h)-pyridine-carboxylate	–	414909-98-1	339.37	3.94	Solid	Pharmaceutical chemicals	GSK
Pluronic L92®	–	–	–	–	–	–	Ryan
p-Methylhydrocinnamic aldehyde	p-Cresyl propionaldehyde	5406-12-2	148.21	2.54	Liquid	–	Gerberick
Potassium dichromate	PDC	7778-50-9	294.18	0.62	Solid	Inorganic Chemical, Chromium Compounds; Inorganic Chemical, Potassium Compounds	NTP, Ryan, Gerberick
Precursor surfactant 1	–	–	–	–	–	–	CESIO
Precursor surfactant 2	–	–	–	–	–	–	CESIO
Propylene glycol	1,2-Dihydroxypropane; 1,2-Propanediol	57-55-6	76.09	0.43	Liquid	Alcohols	Gerberick
Propylparaben	Propyl 4-hydroxybenzoate	94-13-3	180.20	1.77	Solid	Phenols; Carboxylic Acids	Gerberick
p-tert-Butyl-a-ethyl-hydrocinnamal	Lilial	80-54-6	204.31	3.52	Liquid	Aldehydes	Gerberick
p-tert-Butylphenylglycidylether	4-tert-Butylphenyl 2,3-epoxypropyl ether	3101-60-8	206.28	3.52	Liquid	–	BGIA

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Pyridine	–	110-86-1	79.10	1.31	Liquid	Heterocyclic Compounds	Gerberick
Quinoxyfen SC	–	124495-18-7	308.13	5.69	Liquid	Heterocyclic Compounds	ECPA
Quinoxyfen/cyproconazole	–	124495-18-7/ 113096-99-4	308.134/291.776	5.69/ 3.25	Liquid	Heterocyclic Compounds	ECPA
R(+)-Limonene	–	5989-27-5	136.24	2.93	Liquid	Hydrocarbons; Hydrocarbons, Cyclic	Gerberick
R-Carvone	–	2244-16-8	150.22	3.07	Liquid	Hydrocarbons, Other	LLNA/EC3 Validation Study
R-Carvoxime	–	2051-55-0	165.23	3.57	Solid	–	LLNA/EC3 Validation Study
rel-(3r,3as,6ar)-Hexahydrofuro[2,3-b]furan-3-yl 4-nitrophenyl carbonate	–	252873-35-1	295.25	0.83	Solid	Pharmaceutical chemicals	GSK
Resorcinol	1,3-Dihydroxybenzene	108-46-3	110.11	1.17	Solid	Phenols	Basketter
Rifamycin SV	–	14897-39-3	697.77	5.04	Solid	Heterocyclic Compounds, Polycyclic Compounds	NTP
Saccharin	–	81-07-2	183.18	0.64	Solid	Sulfur Compounds; Heterocyclic Compounds	Gerberick
Salicylic acid	2-Hydroxybenzoic acid	69-72-7	138.12	1.03	Solid	Phenols; Carboxylic Acids	Gerberick
Saturated diglycerin	–	–	–	–	–	–	CESIO
Sodium ethyl xanthate	Carbonodithioic acid, O-ethyl ester, sodium salt	140-90-9	144.19	2.11	Solid	Pharmaceutical chemicals	GSK

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Sodium lauroyl lactylate	Pationic 138C	13557-75-0	366.43	2.58	–	–	Gerberick
Sodium lauryl sulfate	Sodium dodecyl sulfate, SLS, SDS, Irium	151-21-3	288.38	1.87/ 1.69	Solid	Alcohols; Sulfur Compounds; Lipids	BGIA, Gerberick
Sodium metasilicate	–	6834-92-0	122.06	-5.65	–	Minerals, Silicon Compounds	NTP
Sodium-3,3,5-trimethylhexanoyloxy-benzenesulfonate	–	94612-91-6	336.38	2.23	–	–	Gerberick
Spearmint oil	–	68917-46-4	–	–	Liquid	–	Lalko & Api
Squalene	2,6,10,15,19,23-Hexamethyl-2,6,10,14,18,22-tetracosahexaene	111-02-4	410.72	14.12	Liquid	Hydrocarbons, Acyclic	EFfCI
Streptomycin sulfate	–	3810-74-0	1457.39	-8.50	Solid	Carbohydrates	Gerberick
Succinic acid	Butanedioic acid	110-15-6	118.09	-0.75	Solid	Carboxylic Acids	EFfCI
Sulfanilamide	4-Aminobenzene-sulfonamide; p-Anilinesulfonamide; p-Sulfamidoaniline	63-74-1	172.21	0.40	Solid	Amides; Sulfur Compounds; Amines	Gerberick
Sulfanilic acid	p-Aminobenzene-sulfonic acid; p-Anilinesulfonic acid	121-57-3	173.19	0.40	Solid	Hydrocarbons, Cyclic; Sulfur Compounds	Gerberick
Tartaric acid	[R-(R*,R*)]-2,3-Dihydroxybutanedioic acid; L-Tartaric acid	87-69-4	150.09	0.87	Solid	Alcohols; Carboxylic Acids	Gerberick
tert-Butyl-3-aminobenzoate	–	92146-82-2	193.25	2.63	Solid	Pharmaceutical chemicals	GSK
Tetramethyl thiuram disulfide	Thiram; Bis (dimethylthio-carbamoyl) disulfide	137-26-8	240.44	1.17	Solid	Carboxylic Acids; Sulfur Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
trans-2-Decenal	–	3913-71-1	154.25	2.54	Liquid	Aldehydes; Hydrocarbons, Other	Gerberick
trans-2-Hexenal	–	6728-26-3	98.15	1.56	Liquid	Heterocyclic Compounds	Gerberick
Trans-2-methyl-2-butenal	–	497-03-0	84.12	1.15	Liquid	Aldehydes	LLNA/EC3 Validation Study
trans-Anethol	–	104-46-1	148.21	2.54	Liquid	Ethers; Phenols	Gerberick
Trienol	17,21-Dihydroxy-16beta-methylpregna-1,4,9(11)-triene-3,20-dione	13504-15-9	356.47	3.02	Solid	Pharmaceutical chemicals	GSK
Trifluralin EC	–	1582-09-8	335.28	5.31	–	Hydrocarbons, Cyclic; Amine	ECPA
Trimethylhexamine diamine	–	–	–	–	–	–	BGIA
Trimethylolpropane Triacrylate	–	15625-89-5	296.32	2.86	Liquid	Carboxylic Acids	NTP
Undec-10-enal	–	112-45-8	168.28	2.79	Liquid	Aldehydes	Gerberick
Undecylenic acid	10-Undecenoic acid	112-38-9	184.28	4.37	Liquid	Lipids	EFfCI
Unsaturated fatty acid	–	–	–	–	–	–	CESIO
Unsaturated fatty acid ester	–	–	–	–	–	–	CESIO
Vanillin	–	121-33-5	152.15	1.28	Solid	Aldehydes	Gerberick
Veratraldehyde	–	120-14-9	166.18	1.45	Solid	Pharmaceutical chemicals	GSK
Vinylidene dichloride	–	75-35-4	96.94	1.45	Liquid	Hydrocarbons, Acyclic; Hydrocarbons, Halogenated	Gerberick
Vinylpyridine	Ethylenepyridine	1337-81-1	105.14	1.80	Liquid	Heterocyclic Compounds	Gerberick

Substance Name	Synonyms	CASRN	Mol. Weight (g/mol)	Log K_{ow}[1,2]	Physical Form	Chemical Class[3]	Data Source
Ylang Ylang (Extra)	Cananga oil; Canangium odoratum genuina oil	8006-81-3	–	–	Liquid	–	Lalko & Api
Ylang Ylang (III)	Cananga oil; Canangium odoratum genuina oil	8006-81-3	–	–	Liquid	–	Lalko & Api

Abbreviations: CASRN = Chemical Abstracts Service Registry Number; g/mol = grams per mole.

[1] K_{ow} represents the octanol-water partition coefficient (expressed on log scale).

[2] When two numbers are shown for K_{ow}, the first number is the value calculated by the method of Moriguchi et al. (1994) and provided in Gerberick et al. (2005). The second number was calculated by the method of Meylan and Howard (1995) and obtained from the website: http://www.srcinc.com/what-we-do/databaseforms.aspx?id=385. LogP (log K_{ow}) values for GSK chemicals were calculated using the method provided by Daylight Chemical Information Systems (see: http://www.daylight.com/dayhtml/doc/clogp/index.html).

[3] Chemical classifications based on the Medical Subject Headings classification for chemicals and drugs, as developed by the National Library of Medicine (available at http://www.nlm.nih.gov/mesh/meshhome.html). Chemical classification of "pharmaceutical chemicals" for the GSK chemicals was suggested by Dr. Michael Olson of GSK, which in spirit captures three types of pharmaceutical active substances (actives, intermediates, and starting materials).

[4] Basketter = Basketter et al. 2007; Bayer = Bayer CropScience SA Studies, submitted by E. Debruyne; BGIA = Berufsgenossenschaftliches Institut fur Arbeitsschutz (German Institute for Occupational Safety and Health) Study Report, submitted by H.W. Vohr; CESIO = Comite Europeen des Agents de Surface et de Leurs Intermediaires Organiques (European Committee of Surfactants and Their Organic Intermediates) Report, submitted by K. Skirda; ECPA = European Crop Protection Association LLNA Project Report, submitted by P. Botham; EFfCI = European Federation for Cosmetic Ingredients study, submitted by P. Ungeheuer; Gerberick = Gerberick et al. 2005; GSK = Glaxo SmithKline, submitted by M.J. Olson; Lalko & Api = Lalko & Api (2006), submitted by A. Api (Research Institute for Fragrance Materials [RIFM]); LLNA/EC3 Validation Study, submitted by D. Basketter, I. Kimber, and F. Gerberick; NTP = NTP Study, submitted by D. Germolec; Ryan = Ryan et al. (2002).

Annex III

Traditional LLNA Data Used for the Performance Analysis of the rLLNA

[This Page Intentionally Left Blank]

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Resorcinol	108-46-3	AOO	+	+	6	1	1.80	2.5	2.30	5.0	2.60	10	6.30	25	10.10	50	12.50	Basketter et al. (2007)
A SC600		PA/H_2O	-	-	NC	10	1.40	25	1.80	50	2.30	100	1.60					Bayer CropScience SA Studies, Submitted by E. Debruyne
AE F016382 00 TK71 A101		PA/H_2O	-	-	NC	3.6	1.00	7.1	0.80	17.9	1.00	35.7	1.10					Bayer CropScience SA Studies, Submitted by E. Debruyne
D EC25®		PA/H_2O	-	-	NC	0.5	0.56	1	0.63	2.5	0.59							Bayer CropScience SA Studies, Submitted by E. Debruyne
D EW 15		PA/H_2O	-	-	NC	2.5	1.90	5	1.50	10	2.50	25	2.50					Bayer CropScience SA Studies, Submitted by E. Debruyne
EXP 10810 A		PA/H_2O	+	+	2.1	10	6.40	25	8.40	50	9.20							Bayer CropScience SA Studies, Submitted by E. Debruyne
EXP 11120 A		PA/H_2O	+	+	64.9	10	0.96	25	0.66	50	1.60	100	6.30					Bayer CropScience SA Studies, Submitted by E. Debruyne
F & Fo WG 50 + 25		PA/H_2O	+	+	0.0031	2.5	11.70	5	12.60	10	14.10	25	15.20					Bayer CropScience SA Studies, Submitted by E. Debruyne
FAR01042-00		PA/H_2O	-	-	NC	10	1.40	25	2.10	50	1.40	100	2.50					Bayer CropScience SA Studies, Submitted by E. Debruyne
FAR01060-00		PA/H_2O	+	+	88.5	10	0.40	25	0.80	50	1.00	100	3.60					Bayer CropScience SA Studies, Submitted by E. Debruyne
Fx + Me EW 69		PA/H_2O	+	+	25.2	5	0.83	10	1.55	25	2.95	50	8.55					Bayer CropScience SA Studies, Submitted by E. Debruyne
1-(2,3-epoxypropoxy)-2,2-bis [(2,3-epoxypropoxy)-methylbutane		ACE	+	+	1.4	1	2.06	3	6.52	10	12.00							BGIA Study Report, Submitted by H.W. Vohr
1,2-Diaminocyclo-hexane	1436-59-5	ACE	+	+	0.4	0.1	1.19	0.3	1.81	1	8.39							BGIA Study Report, Submitted by H.W. Vohr

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
1,6-Bis(2,3-epoxypropoxy)-hexane	16096-31-4	ACE	+	+	1.9	0.3	0.94	1	1.67	3	4.65							BGIA Study Report, Submitted by H.W. Vohr
3-Aminomethyl-3,5,5-trimethylcyclohexyl amine	2855-13-2	ACE	+	+	1.0	0.3	1.17	1	2.68	3	20.16							BGIA Study Report, Submitted by H.W. Vohr
Bakelite EPR 161	9012-45-7	ACE	+	+	0.7	0.1	1.02	0.3	2.37	1	3.49							BGIA Study Report, Submitted by H.W. Vohr
Bakelite EPR 162	9012-45-7	ACE	+	+	0.1	0.3	10.53	1	19.94	3	39.89							BGIA Study Report, Submitted by H.W. Vohr
Bakelite EPR 164	9012-45-7	ACE	+	+	0.2	0.3	5.58	1	16.11	3	28.13							BGIA Study Report, Submitted by H.W. Vohr
Dipropylene triamine	56-18-8	ACE	+	+	0.9	0.3	2.16	1	3.17	3	12.45							BGIA Study Report, Submitted by H.W. Vohr
Hexyl cinnamic aldehyde	101-86-0	AOO	-	-	NC	2.5	1.12	5	1.19	10	2.84							BGIA Study Report, Submitted by H.W. Vohr
Hexyl cinnamic aldehyde	101-86-0	ACE	+	+	1.2	3	4.56	10	6.63	30	9.86							BGIA Study Report, Submitted by H.W. Vohr
Hydroxyethyl-ethylenediamine	111-41-1	ACE	+	+	IDR[3]	3	2.00	10	1.72	30	6.60							BGIA Study Report, Submitted by H.W. Vohr
m-Phenylenebis-(methylamine)	1477-55-0	ACE	+	+	0.4	0.3	1.92	1	9.09	3	44.20							BGIA Study Report, Submitted by H.W. Vohr
Oxirane, mono((C12-14-alkyloxy)methyl) derivs	68609-97-2	ACE	+	+	0.6	0.3	2.35	1	4.16	3	22.74							BGIA Study Report, Submitted by H.W. Vohr
p-tert-Butylphenyl-glycidylether	3101-60-8	ACE	+	+	0.4	0.1	1.36	0.3	1.68	1	14.22							BGIA Study Report, Submitted by H.W. Vohr
Sodium lauryl sulfate	151-21-3	Pluronic L92	+	+	4.9	5	3.05	10	4.78	25	8.46							BGIA Study Report, Submitted by H.W. Vohr
Trimethylhexamine diamine		ACE	+	+	1.9	1	2.15	3	4.00	10	8.86							BGIA Study Report, Submitted by H.W. Vohr
Benzalkonium chloride	8001-54-5	ACE	+	+	0.1	0.5	9.00	1	11.10	2	7.60							CESIO Report, Submitted by K. Skirda

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Fatty acid glutamate			+	+	IDR[3]	5	1.50	25	1.80	50	1.20	100	4.80					CESIO Report, Submitted by K. Skirda
Glyceryl thioglycolate	30618-84-9	AOO	+	+	4.7	10	8.00	25	14.00	50	31.00							CESIO Report, Submitted by K. Skirda
Laurylglycerin derivative		DMF	+	+	24.3	5	1.62	10	2.36	25	3.03							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 1		AOO	+	+	27.5	25	2.80	50	4.80	100	6.50							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 2		AOO	-	+	47.1	25	1.50	50	3.20	100	2.90							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 3		AOO	+	+	19.8	25	4.70	50	9.80	100	13.30							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 4		AOO	+	+	0.012	25	36.00	50	39.00	100	162.00							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 5		AOO	+	+	37.5	25	2.70	50	3.30	100	3.20							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 6		AOO	+	+	34.4	25	2.70	50	3.50	100	6.50							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 7		AOO	+	+	IDR[3]	25	6.30	50	50.80	100	7.40							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 8		AOO	+	+	IDR[3]	25	4.20	50	3.30	100	5.60							CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 9		AOO	+	+	10.5	25	3.50	50	3.90	100	7.70							CESIO Report, Submitted by K. Skirda
Precursor surfactant 1		AOO	+	+	60.7	25	2.20	50	2.70	100	4.10							CESIO Report, Submitted by K. Skirda
Precursor surfactant 2		AOO	+	+	24.0	25	3.10	50	4.80	100	4.40							CESIO Report, Submitted by K. Skirda
Saturated diglycerin		EtOH/ H_2O	-	-	NC	25	1.40	50	2.10	100	1.90							CESIO Report, Submitted by K. Skirda
Unsaturated fatty acid		AOO	+	+	22.2	25	3.40	50	5.70	100	6.50							CESIO Report, Submitted by K. Skirda

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Unsaturated fatty acid ester		AOO	+	+	27.1	25	2.80	50	5.20	100	4.70							CESIO Report, Submitted by K. Skirda
Atrazine SC	1912-24-9	Pluronic L92 (1%)	+	+	31.3	12.5	1.80	25	2.80	50	3.60	75	7.10	100	7.30			ECPA LLNA Project Report, Submitted by P. Botham
Dinocap EC	39300-45-3	Pluronic L92 (1%)	+	+	1.1	0.8	2.00	4	14.20	21	26.70							ECPA LLNA Project Report, Submitted by P. Botham
Oxyfluorfen EC	42874-03-3	Pluronic L92 (1%)	-	-	NC	1	0.30	7	0.90	33	2.30							ECPA LLNA Project Report, Submitted by P. Botham
Quinoxyfen SC	124495-18-7	Pluronic L92 (1%)	-	-	NC	7	1.10	33	1.70	100	0.80							ECPA LLNA Project Report, Submitted by P. Botham
Quinoxyfen/ cyproconazole	124495-18-7/ 113096-99-4	Pluronic L92 (1%)	+	+	27.8	12.5	2.00	25	2.30	50	8.60	75	15.80	100	30.10			ECPA LLNA Project Report, Submitted by P. Botham
Trifluralin EC	1582-09-8	Pluronic L92 (1%)	+	+	7.0	7	3.10	33	26.30	100	61.50							ECPA LLNA Project Report, Submitted by P. Botham
Fumaric acid	110-17-8	DMSO	-	-	NC	5	1.30	10	2.30	25	1.40							EFfCI study, Submitted by P. Ungeheuer
Linoleic acid	60-33-3	AOO	+	+	14.1	10	1.50	25	7.00	50	9.10							EFfCI study, Submitted by P. Ungeheuer
Linolenic acid	463-40-1	AOO	+	+	9.9	10	3.10	25	9.30	50	10.30							EFfCI study, Submitted by P. Ungeheuer
Maleic acid	110-16-7	DMSO	+	+	7.0	10	6.70	25	16.10	50	16.10							EFfCI study, Submitted by P. Ungeheuer
Octinol	111-87-5	AOO	+	+	4.7	10	5.60	25	8.80	50	11.20							EFfCI study, Submitted by P. Ungeheuer
Oleic acid	112-80-1	AOO	+	+	10.5	10	2.60	25	14.90	50	6.90							EFfCI study, Submitted by P. Ungeheuer
Squalene	111-02-4	AOO	+	+	7.9	10	3.80	25	6.90	50	8.20							EFfCI study, Submitted by P. Ungeheuer

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Succinic acid	110-15-6	DMSO	-	-	NC	5	1.20	10	1.20	25	1.30							EFfCI study, Submitted by P. Ungeheuer
Undecylenic acid	112-38-9	AOO	+	+	19.4	10	2.50	25	3.30	50	4.40							EFfCI study, Submitted by P. Ungeheuer
1-(2',3',4',5'-Tetramethylphenyl) -3-(4'-tetrabutylphenyl)-propane-1,3-dione		ACE	-	-	NC	10	1.60	20	1.20	40	1.60							Gerberick et al. (2005)
1-(2',3',4',5'-Tetramethylphenyl) butane-1,3-dione	167998-73-4	ACE	+	+	8.3	10	7.00	20	22.10	40	22.40							Gerberick et al. (2005)
1-(2',5' Dimethylphenyl) butane-1,3-dione	56290-55-2	ACE	+	+	12.5	10	2.3	20	5.1	40	9.5							Gerberick et al. (2005)
1-(2',5'-diethylphenyl) butane-1,3,-dione	167998-76-7	ACE	+	+	9.6	10	3.9	20	19.2	40	18.7							Gerberick et al. (2005)
1-(3',4',5'-Tetramethoxy-phenyl)-4-dimethylpentane-1,3-dione	135099-98-8	ACE	-	-	NC	10	2.80	20	1.10	40	0.70							Gerberick et al. (2005)
1-(p-methoxyphenyl)-1-penten-3-one	104-27-8	AOO	+	+	9.3	10	3.5	25	10	50	26.1							Gerberick et al. (2005)
1,1,3-Trimethyl-2-formyylcyclohexa-2,4-dione	116-26-7	AOO	+	+	7.5	0.5	0.70	1	1.10	2.5	1.10	5	2.70	10	3.30			Gerberick et al. (2005)
1,2-Benzisothiazolin-3-one	2634-33-5	DMF	+	+	2.3	10	3.80	30	4.40	50	4.90							Gerberick et al. (2005)
1,2-Dibromo-2,4-dicyanobutane	35691-65-7	AOO	+	+	0.9	0.5	1.40	1	3.40	2.5	3.50	5	5.40					Gerberick et al. (2005)
1,4-dihydroquinone	123-31-9	AOO	+	+	0.1	0.1	2.80	0.25	5.80	0.5	13.70	1	15.20	2.5	13.10			Gerberick et al. (2005)
12-Bromo-1-dodecanol	3344-77-2	AOO	+	+	6.9	5	2.20	10	4.3	25	9.8							Gerberick et al. (2005)
12-Bromododecanoic acid	73367-80-3	AOO	+	+	17.9	5	1.30	10	2.00	25	3.9							Gerberick et al. (2005)
1-Bromobutane	109-65-9	AOO	-	-	NC	5	1.1	10	1.2	25	1							Gerberick et al. (2005)
1-Bromodocosane	6938-66-5	AOO	+	+	8.3	2.5	1.2	5	1.6	10	3.7							Gerberick et al. (2005)
1-Bromododecane	143-15-7	AOO	+	+	17.7	5	1.1	10	1.4	25	4.5							Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
1-Bromoeicosane	4276-49-7	AOO	+	+	6.1	5	2.1	10	6.2	25	8.4							Gerberick et al. (2005)
1-Bromoheptadecane	3508-00-7	AOO	+	+	4.8	5	3.2	10	6	25	9.6							Gerberick et al. (2005)
1-Bromohexadecane	112-82-3	AOO	+	+	2.3	1	1.1	2.5	3.3	5	7.9	10	11.1	25	13.5	50	16.8	Gerberick et al. (2005)
1-Bromohexane	111-25-1	AOO	+	+	10.3	1	1.7	10	2.9	50	18.6							Gerberick et al. (2005)
1-Bromononane	693-58-3	AOO	-	-	NC	5	1.2	10	1.4	25	2.8							Gerberick et al. (2005)
1-Bromooctadecane	112-89-0	AOO	+	+	15.2	5	1.8	10	2.2	25	4.5							Gerberick et al. (2005)
1-Bromopentadecane	629-72-1	AOO	+	+	5.1	5	2.9	10	7.8	25	19.6							Gerberick et al. (2005)
1-Bromotetradecane	112-71-0	AOO	+	+	9.2	5	1.5	10	3.3	25	11.3							Gerberick et al. (2005)
1-Bromotridecane	765-09-3	AOO	+	+	10.2	5	1.6	10	2.9	25	10.4							Gerberick et al. (2005)
1-Bromoundecane	693-67-4	AOO	+	+	19.6	5	1.3	10	1.4	25	3.9							Gerberick et al. (2005)
1-Butanol	71-36-3	dH_2O	-	-	NC	5	1.6	10	1.2	20	1.4							Gerberick et al. (2005)
1-Chloro-2,4-dinitrobenzene	97-00-7	AOO	+	+	0.05	0.01	1.50	0.025	1.8	0.05	2.4	0.1	8.9	0.25	38			Gerberick et al. (2005)
1-Chlorohexadecane	4860-03-1	AOO	+	+	9.1	5	1.6	10	3.3	25	5.7							Gerberick et al. (2005)
1-Chloromethyl-pyrene	1086-00-6	AOO	+	+	0.005	0.025	11.6	0.05	15.4	0.1	18.6							Gerberick et al. (2005)
1-Chlorononane	2473-01-0	AOO	-	-	NC	10	1	25	1.6	50	2.3							Gerberick et al. (2005)
1-Chlorooctadecane	3386-33-2	AOO	+	+	16.3	10	1.7	25	4.8	50	7.3							Gerberick et al. (2005)
1-Chlorotetradecane	2425-54-9	AOO	+	+	20.2	10	1.1	25	3.9	50	6.3							Gerberick et al. (2005)
1-Iododecane	4292-19-7	AOO	+	+	13.1	5	1.70	10	2.30	25	5.70							Gerberick et al. (2005)
1-Iodohexadecane	544-77-4	AOO	+	+	19.1	10	1.60	25	3.90	50	6.40							Gerberick et al. (2005)
1-Iodohexane	638-45-9	AOO	-	-	NC	10	0.90	25	1.20	50	2.50							Gerberick et al. (2005)
1-Iodononane	4282-42-2	AOO	+	+	24.2	10	1.30	25	3.10	50	4.60							Gerberick et al. (2005)
1-Iodooctadecane	629-93-6	AOO	-	-	NC	5	1	10	1.4	25	1.9							Gerberick et al. (2005)
1-Iodotetradecane	19218-94-1	AOO	+	+	13.8	10	1.70	25	6.90	50	9.70							Gerberick et al. (2005)
1-Methyl-3-nitro-nitrosoguanidine	70-25-7	AOO	+	+	0.03	0.05	27.5	0.1	60.4	0.25	78.3							Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
1-Napthol	90-15-3	AOO	+	+	1.3	0.1	1.40	0.25	1.00	0.5	1.20	1	1.50	2.5	8.50			Gerberick et al. (2005)
1-Phenyl-1,2-propanedione	579-07-7	AOO	+	+	1.3	5	12.80	10	17.70	25	20.10							Gerberick et al. (2005)
1-Phenyl-2-methylbutane-1,3-dione	6668-24-2	ACE	+	+	29.1	10	1.70	20	2.00	40	4.20							Gerberick et al. (2005)
1-Phenyloctane--1,3-dione	55846-68-1	ACE	+	+	10.4	10	2.80	20	6.60	40	8.70							Gerberick et al. (2005)
2-(4-Amino-2nitro-phenylamino)-ethanol	2871-01-4	AOO	+	+	2.2	0.1	0.50	0.25	1.20	0.5	1.90	1	1.8	2.5	3.3			Gerberick et al. (2005)
2-(4-tert-Amylcyclohexyl) acetaldehyde	620159-84-4	AOO	+	+	36.8	25	2.1	50	4.00	100	9.10							Gerberick et al. (2005)
2,2,6,6-Tetramethyl-heptane-3,5-dione	1118-71-4	ACE	+	+	26.7	10	2.10	20	2.80	40	3.40							Gerberick et al. (2005)
2,3-Butanedione	431-03-8	AOO	+	+	11.3	5	1.4	10	2.8	25	5.2							Gerberick et al. (2005)
2,4,6-Trichloro-1,3,5-triazine	108-77-0	AOO	+	+	0.09	1	21.80	2.5	28.90	5	34.00							Gerberick et al. (2005)
2,4-Heptadienal	5910-85-0	AOO	+	+	4.0	0.5	1.1	1	1.4	2.5	1.9	5	3.7	10	8.10			Gerberick et al. (2005)
2,5-Diaminotoluene	95-70-5	DMSO	+	+	0.17	0.125	2.6	0.25	3.5	0.5	4.1	1	5.5					Gerberick et al. (2005)
2-Acetylcyclo-hexanone	874-23-7	ACE	-	-	NC	10	0.8	20	0.7	40	0.8							Gerberick et al. (2005)
2-Amino-6-chloro-4-nitrophenol	6358-09-4	AOO	+	+	2.2	0.1	1.7	0.25	1.4	0.5	2.1	1	1.5	2.5	3.4			Gerberick et al. (2005)
2-Aminophenol	95-55-6	AOO	+	+	0.4	0.5	3.5	1	5	2.5	7.4							Gerberick et al. (2005)
2-Bromotetra-decanoic acid	10520-81-7	AOO	+	+	3.4	5	4.7	10	7.7	25	10.1							Gerberick et al. (2005)
2-Hydroxyethyl acrylate	818-61-1	AOO	+	+	1.4	5	10.70	10	14.80	25	18.10							Gerberick et al. (2005)
2-Hydroxypropyl methacrylate	923-26-2	AOO	-	-	NC	10	1.1	25	1.2	50	1.3							Gerberick et al. (2005)
2-Mercapto-benzothiazole	149-30-4	DMF	+	+	1.7	1	2.3	3	4.4	10	8.6							Gerberick et al. (2005)
2-Methoxy-4-methylphenol	93-51-6	AOO	+	+	5.8	4.2	1.80	8.4	5.00	21	8.50							Gerberick et al. (2005)
2-Methyl-2H-isothiazol-3-one	2682-20-4	AOO	-	+	1.9	0.25	1.50	0.5	1.50	1	1.8	2.5	3.8	5	2.5			Gerberick et al. (2005)
2-Methyl-4H,3,1-benzoxazin-4-one	525-76-8	DMSO	+	+	0.7	5	7.60	10	9.20	25	10.80							Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
2-Methyl-5-hydroxy-ethylaminophenol	55302-96-0	AOO	+	+	0.4	0.1	1.20	0.25	0.80	0.5	3.60	1	2.6	2.5	7.4			Gerberick et al. (2005)
2-Methylundecanal	110-41-8	AOO	+	+	10.0	0.5	1.40	1	1.30	2.5	1.30	5	2.40	10	3.00			Gerberick et al. (2005)
2-Nitro-p-phenylenediamine	5307-14-2	AOO	+	+	0.4	0.1	1.80	0.25	2.20	0.5	3.30	1	7.90	2.5	11.90			Gerberick et al. (2005)
3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexane-1-carboxaldehyde	31906-04-4	AOO	+	+	17.1	1	0.60	2.5	0.70	5	0.60	10	1.30	25	4.90			Gerberick et al. (2005)
3, 3', 4', 5-Tetrachloro-salicylanilide	1154-59-2	ACE	+	+	0.04	0.25	11.20	0.5	14.40	1	18.00							Gerberick et al. (2005)
3,4-Dihydrocoumarin	119-84-6	AOO	+	+	5.6	2.5	1.6	5	2.5	10	6.6							Gerberick et al. (2005)
3,5,5-Trimethyl-hexanoyl chloride	36727-29-4	AOO	+	+	2.7	5	7.20	10	12.00	25	19.00							Gerberick et al. (2005)
3-Aminophenol	591-27-5	AOO	+	+	3.2	2.5	2.8	5	3.5	10	5.7							Gerberick et al. (2005)
3-Bromomethyl-5, 5'-dimethyl-dihydro-2(3H)-furanone	154750-20-6	AOO	+	+	**3.5**	3.19	2.7	6.37	5.1	12.74	7.1							Gerberick et al. (2005)
3-Dimethylamino-propylamine	109-55-7	AOO	+	+	2.2	0.5	1.30	1	1.10	2.5	3.50	5	7.00	10	13.90			Gerberick et al. (2005)
3-Ethoxy-1-(2',3',4',5'-tetramethylphenyl)propane-1,3-dione	170928-69-5	ACE	+	+	33	10	1.1	20	1.7	40	3.7							Gerberick et al. (2005)
3-Methyl-4-phenyl-1,2,5-thiadiazole-1,1-dioxide	3775-21-1	AOO	+	+	1.4	0.1	1.3	0.25	1.1	0.5	2.1	1	1.9	2.5	5.6			Gerberick et al. (2005)
3-Methyleugenol	186743-26-0	AOO	+	+	32	11	1.5	27	2.3	54	6.4							Gerberick et al. (2005)
3-Methylisoeugenol	186743-29-3	AOO	+	+	3.6	2.5	2.20	5.5	4.30	11	6.00							Gerberick et al. (2005)
3-Phenylene-diamine	108-45-2	AOO	+	+	0.5	2.5	11.70	5	15.50	10	19.20							Gerberick et al. (2005)
3-Propyliden-phthalide	17369-59-4	AOO	+	+	3.7	5	4.90	10	9.10	25	15.10							Gerberick et al. (2005)
4-(N-Ethyl-N-2-methan-sulfamido-ethyl)-2-methyl-1,4,-phenylene-diamine	25646-71-3	DMSO	+	+	0.6	0.1	1.2	1	4.5	5	5.9	10	6.3					Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
4,4,4-Trifluoro-1-phenylbutane-1,3-dione	362-06-7	ACE	+	+	20	10	2.10	20	3.00	40	4.60							Gerberick et al. (2005)
4-Allylanisole	140-67-0	AOO	+	+	18	10	1.20	25	4.7	50	4.5	100	8					Gerberick et al. (2005)
4-Hydroxybenzoic acid	99-96-7	DMSO	-	-	NC	5	1.4	10	1.5	25	1.3							Gerberick et al. (2005)
4'-Methoxy-acetophenone	100-06-1	AOO	-	-	NC	10	1.3	25	1	50	1							Gerberick et al. (2005)
4-Methylamino-phenol sulfate	55-55-0	DMF	+	+	0.8	0.5	2.50	1	3.40	2.5	6.70							Gerberick et al. (2005)
4-Nitrobenzyl bromide	100-11-8	AOO	+	+	0.05	0.01	0.90	0.03	1.30	0.05	3.50	0.1	11.50					Gerberick et al. (2005)
4-Phenylene-diamine	106-50-3	AOO	+	+	0.16	0.05	1.90	0.1	2.30	0.25	4.00	0.5	5.70	1.0	6.60			Gerberick et al. (2005)
5,5-Dimethyl-3-methylenedihydro-2(3H)-furanone	29043-97-8	AOO	+	+	**2.0**	2	3	4	7.4	8	9.2							Gerberick et al. (2005)
5-Chloro-2-methyl-4-isothiazolin-3-one	26172-55-4	DMF	+	+	0.009	0.01	3.50	0.03	12.30	0.1	22.70							Gerberick et al. (2005)
5-Methyl-2,3-hexanedione	13706-86-0	AOO	+	+	26	25	2.90	50	6.00	100	14.30							Gerberick et al. (2005)
5-Methyleugenol	186743-25-9	AOO	+	+	13	11	2.7	27	4.9	54	4.3							Gerberick et al. (2005)
6-Methylcoumarin	92-48-8	ACE	-	-	NC	5	1	10	1	25	1.1							Gerberick et al. (2005)
6-Methyleugenol	186743-24-8	AOO	+	+	17	11	1.9	27	4.9	54	8.3							Gerberick et al. (2005)
6-Methylisoeugenol	13041-12-8	AOO	+	+	1.6	2.5	5.90	5.5	11.10	11	15.7							Gerberick et al. (2005)
7,12-Dimethyl-benz[a]anthracene	57-97-6	DMF	+	+	0.006	0.025	7.60	0.5	17.70	1	15.60							Gerberick et al. (2005)
7-Bromotetradecane	74036-97-8	AOO	+	+	21	5	0.9	10	1.2	25	3.6							Gerberick et al. (2005)
Abietic acid	514-10-3	AOO	+	+	15	5	1.5	10	2	25	5.2							Gerberick et al. (2005)
alpha-Amyl cinnamic aldehyde	122-40-7	AOO	+	+	10.6	1	1.5	2.5	1.7	5	2.2	10	2.8	25	8.2			Gerberick et al. (2005)
alpha-Butyl cinnamic aldehyde	7492-44-6	AOO	+	+	11.2	1	1.4	2.5	1.7	5	1.7	10	2.1	25	13			Gerberick et al. (2005)
alpha-Methyl cinnamic aldehyde	101-39-3	AOO	+	+	4.5	1	1.80	2.5	1.50	5	3.40	10	3.3	25	15.3			Gerberick et al. (2005)
alpha-Methylphenyl-acetaldehyde	93-53-8	AOO	+	+	6.3	0.5	2	1	2.2	2.5	1	5	2.2	10	5.2			Gerberick et al. (2005)
Aniline	62-53-3	AOO	+	+	89	5	1.1	10	0.9	25	2	50	1.9	100	3.3			Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Benzaldehyde	100-52-7	AOO	-	-	NC	1	2.1	2.5	1.7	5	2.2	10	1.8	25	2			Gerberick et al. (2005)
Benzene-1,3,4-tricarboxylic anhydride	552-30-7	AOO	+	+	9.2	1	1.10	2.5	2.00	5	2.00	10	3.20	25	4.60			Gerberick et al. (2005)
Benzo[a]pyrene	50-32-8	AOO	+	+	0.0009	0.5	17.6	1	19.2	2.5	27							Gerberick et al. (2005)
Benzocaine	94-09-7	AOO	-	-	NC	2.5	2.1	5	1.8	10	2.7	25	1.8	50	1.2			Gerberick et al. (2005)
Benzoquinone	106-51-4	AOO	+	+	0.0099	0.5	36.4	1	42.3	2.5	52.3							Gerberick et al. (2005)
Benzyl benzoate	120-51-4	AOO	+	+	17	5	2.3	25	3.5									Gerberick et al. (2005)
Benzyl bromide	100-39-0	AOO	+	+	0.2	0.25	3.5	0.5	11.5	1	16.1	2.5	16.4	5	25.1			Gerberick et al. (2005)
Benzylidene acetone	122-57-6	AOO	+	+	3.7	10	8.5	25	13.6	50	12.8							Gerberick et al. (2005)
beta-Propiolactone	57-57-8	AOO	+	+	0.15	0.025	1.50	1.0	13.00	2.5	19.90							Gerberick et al. (2005)
bis-1,3-(2',5'-dimethylphenyl)-propane-1,3-dione		ACE	-	-	NC	10	1.8	20	1.6	40	2.1							Gerberick et al. (2005)
Bisphenol A-diglycidyl ether	1675-54-3	AOO	+	+	1.5	1	2	3	6	10	17.4							Gerberick et al. (2005)
Butyl glycidyl ether	2426-08-6	AOO	+	+	30.9	10	1.40	25	2.20	50	5.60							Gerberick et al. (2005)
C11-azlactone	176665-06-8	AOO	+	+	16	8.3	1.30	20.7	4.00	41.3	8.50							Gerberick et al. (2005)
C15-azlactone	176665-09-1	AOO	+	+	18	10	1.80	25	4.10	50	7.50							Gerberick et al. (2005)
C17-azlactone	176665-11-5	AOO	+	+	19	10.87	1.70	27.17	4.30	54.33	4.60							Gerberick et al. (2005)
C19-azlactone		AOO	-	+	26	11.73	2.50	29.33	3.10	58.67	2.50							Gerberick et al. (2005)
C4-azlactone	176664-99-6	AOO	+	+	1.4	0.52	1.10	1.31	2.30	2.62	4.10	5.23	11.70					Gerberick et al. (2005)
C6-azlactone	176665-02-4	AOO	+	+	1.3	0.61	1.20	1.52	3.50	3.05	7.60							Gerberick et al. (2005)
C9-azlactone	176665-04-6	AOO	+	+	2.8	1.85	1.40	3.7	4.60	7.4	10.10							Gerberick et al. (2005)
Camphorquinone	465-29-2	AOO	-	+	10	5	2.8	10	3	25	1.7							Gerberick et al. (2005)
Chlorobenzene	108-90-7	AOO	-	-	NC	5	1.1	10	1.7	25	1.6							Gerberick et al. (2005)
Cinnamic alcohol	104-54-1	AOO	+	+	21	10	1.8	25	3.5	50	3.9	90	5.7					Gerberick et al. (2005)
Cinnamic aldehyde	104-55-2	AOO	+	+	3.0	0.5	1.40	1.0	0.90	2.5	1.90	5.0	7.10	10.0	15.80			Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
cis-6-Nonenal	2277-19-2	AOO	+	+	22	10	1.60	25.0	3.30	50.0	4.50	100.0	13.70					Gerberick et al. (2005)
Citral	5392-40-5	AOO	+	+	13	5	1.20	10	2.10	25	6.30							Gerberick et al. (2005)
Clotrimazole	23593-75-1	AOO	+	+	4.8	2.5	1.6	5	3.1	10	3							Gerberick et al. (2005)
Coumarin	91-64-5	AOO	-	-	NC	5	2.70	10	2.90	25	2.30							Gerberick et al. (2005)
Cyclamen aldehyde	103-95-7	AOO	+	+	22.0	1	1.40	2.5	1.30	10	1.80	25	3.3	50	5.2			Gerberick et al. (2005)
Diethyl maleate	141-05-9	AOO	+	+	5.8	25	16.30	50	22.60	100	13.10							Gerberick et al. (2005)
Diethyl sulfate	64-67-5	AOO	+	+	3.3	1	0.8	2.5	1.9	10	12							Gerberick et al. (2005)
Diethyl-acetaldehyde	97-96-1	AOO	+	+	76	25	1.2	50	0.8	75	2.4	100	16.3					Gerberick et al. (2005)
Diethylenetriamine	111-40-0	AOO	+	+	5.8	10	6.40	25	12.10									Gerberick et al. (2005)
Diethylpthalate	84-66-2	AOO	-	-	NC	25	1.00	50	1.30	100	1.50							Gerberick et al. (2005)
Dihydroeugenol	2785-87-7	AOO	+	+	6.8	5.1	2.70	10.1	3.60	25.3	7.80							Gerberick et al. (2005)
Dimethyl sulfate	77-78-1	AOO	+	+	0.19	0.25	3.80	0.5	6.00	1	5.70							Gerberick et al. (2005)
Dimethyl sulfoxide	67-68-5	AOO	+	+	72	25	2.70	50	2.30	100	3.90							Gerberick et al. (2005)
Dodecyl methanesulfonate	51323-71-8	AOO	+	+	8.8	5	2.10	10	3.30	25	9.00							Gerberick et al. (2005)
Ethyl benzoylacetate	94-02-0	ACE	-	-	NC	10	0.9	20	0.9	40	1.2							Gerberick et al. (2005)
Ethyl vanillin	121-32-4	AOO	-	-	NC	2.5	0.65	5	1.05	10	0.74	25	0.36	50	0.29			Gerberick et al. (2005)
Ethyl acrylate	140-88-5	AOO	+	+	28	10	1.2	25	2.7	50	5							Gerberick et al. (2005)
Ethylene glycol dimethacrylate	97-90-5	MEK	+	+	28	10	1.20	25	2.40	50	7.00							Gerberick et al. (2005)
Ethylenediamine free base	107-15-3	AOO	+	+	2.2	0.1	1.10	0.25	1.20	0.5	1.60	1	1.90	2.5	3.30	5	6.10	Gerberick et al. (2005)
Eugenol	97-53-0	AOO	+	+	13	2.5	1.60	5	1.50	10	2.40	25	5.50					Gerberick et al. (2005)
Farnesal	502-67-0	AOO	+	+	12	1	0.60	2.5	1.10	5	1.70	10	2.50	25	7.00			Gerberick et al. (2005)
Fluorescein isothiocyanate	27072-45-3	ACE/ DBP (50:50)	+	+	0.143	0.5	8.60	1	11.70	2.5	16.60							Gerberick et al. (2005)
Formaldehyde	50-00-0	ACE	+	+	0.61	0.093	1.10	0.185	2.30	0.37	2.30	0.925	3.90	1.85	4.00			Gerberick et al. (2005)
Furil	492-94-4	AOO	-	-	NC	5	1.20	10	1.70	25	2.20							Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Geraniol	106-24-1	EtOH/ DEP (75:25)	+	+	26	1	1.00	3	1.00	10	1.30	30	3.40	50	3.90			Gerberick et al. (2005)
Glutaraldehyde	111-30-8	ACE	+	+	0.1	0.05	1.30	0.125	4.30	0.25	7.60	0.5	11.60	1.25	17.70	2.5	18.00	Gerberick et al. (2005)
Glycerol	56-81-5	DMF	-	-	NC	25	1.10	50	0.70	100	0.50							Gerberick et al. (2005)
Glyoxal	107-22-2	AOO	+	+	1.4	1	2.50	2.5	4.20	5	5.20	10	10.30	25	15.80			Gerberick et al. (2005)
Hexane	110-54-3	AOO	-	-	NC	25	0.8	50	0.8	100	2.2							Gerberick et al. (2005)
Hexyl cinnamic aldehyde	101-86-0	AOO	+	+	11	2.5	1.30	5	1.10	10	2.50	25	10.00	50	17.00			Gerberick et al. (2005)
Hydroxycitronellal	107-75-5	AOO	+	+	33	2.5	2.20	5	1.00	10	0.80	25	1.10	50	7.10			Gerberick et al. (2005)
Imidazolidinyl urea	39236-46-9	DMF	+	+	24	10	1.70	25	3.10	50	5.50							Gerberick et al. (2005)
Isoeugenol	97-54-1	AOO	+	+	1.7	0.5	1.00	1	1.10	5	12.40							Gerberick et al. (2005)
Isononanoyl chloride	57077-36-8	AOO	+	+	2.7	5	6.60	10	10.60	25	12.60							Gerberick et al. (2005)
Isopropanol	67-63-0	AOO	-	-	NC	10	1.7	25	1.1	50	1							Gerberick et al. (2005)
Isopropyl myristate	110-27-0	AOO	+	+	44	25	2.10	50	3.30	100	3.40							Gerberick et al. (2005)
Isopropyleugenol	51474-90-9	AOO	-	-	NC	12	1.8	29.0	1.8	59.0	2.2							Gerberick et al. (2005)
Isopropyl-isoeugenol	2953-00-7	AOO	+	+	0.6	0.6	3.00	1.2	5.70	3.0	10.70							Gerberick et al. (2005)
Kanamycin	59-01-8; 8063-07-8	AOO	-	-	NC	5	2.2	10	0.8	25	1							Gerberick et al. (2005)
Lactic acid	598-82-3	DMSO	-	-	NC	5	1	10	1.4	25	2.2							Gerberick et al. (2005)
Lauryl gallate	1166-52-5	DMSO	+	+	0.3	1	12.10	10	29.70	25	29.30	50	36					Gerberick et al. (2005)
Linalool alcohol	78-70-6	AOO	+	+	30	25	2.5	50	4.8	100	8.3							Gerberick et al. (2005)
Methyl dodecanesulfonate	2374-65-4	AOO	+	+	0.4	1	21.6	2.5	39.9	5	48.6							Gerberick et al. (2005)
Methyl hexacecyl sulfonate	4230-15-3	AOO	-	-	NC	5	1	10	1.3	25	1.5							Gerberick et al. (2005)
Methyl hexadecane-sulfonate	26452-48-2	AOO	+	+	0.8	5	26.7	10	35.4	25	32.9							Gerberick et al. (2005)
Methyl methanesulfonate	66-27-3	AOO	+	+	2.7	0.25	0.7	1	0.7	10	3.6							Gerberick et al. (2005)
Methyl salicylate	119-36-8	AOO	-	-	NC	1.0	1	2.5	1.1	5.0	1.6	10	1.4	20	0.9			Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Methyl(2-sulfomethyl) octadecanoate		AOO	+	+	2.0	2.5	5.10	5.0	11.60	10.0	25.60							Gerberick et al. (2005)
Methyl-2-nonynoate	111-80-8	EtOH (80%)	+	+	2.5	5	10.4	10	17.7	20	24.4							Gerberick et al. (2005)
Methyl-4-hydroxybenzoate	99-76-3	DMF	-	-	NC	10	0.80	25	0.90	50	0.80							Gerberick et al. (2005)
N-Ethyl-N-nitrosourea	759-73-9	AOO	+	+	1.1	0.25	1.00	1	2.70	10	22.30							Gerberick et al. (2005)
N-Methyl-N-nitrosourea	684-93-5	AOO	+	+	0.05	0.05	2.7	0.1	7.1	0.25	15.4							Gerberick et al. (2005)
Nonanoyl chloride	764-85-2	AOO	+	+	1.8	5	12.70	10	19.40	25	20.90							Gerberick et al. (2005)
Octanoic acid	124-07-2	AOO	-	-	NC	10	0.70	25.0	1.00	50.0	1.60							Gerberick et al. (2005)
Oleyl methane sulfonate	35709-09-2	AOO	+	+	25	5	1.00	10.0	1.30	25.0	3.00							Gerberick et al. (2005)
Oxalic acid	144-62-7	DMF	+	+	15	5	2.40	10	2.80	25	3.40							Gerberick et al. (2005)
Oxazolone	15646-46-5	AOO	+	+	0.003	0.003	2.90	0.005	4.90	0.01	12.00	0.025	22.00	0.05	33.00			Gerberick et al. (2005)
Palmitoyl chloride	112-67-4	AOO	+	+	8.8	5	2.10	10	3.30	25	4.50							Gerberick et al. (2005)
Penicillin G	61-33-6	DMSO	+	+	30	2.5	1.00	5.0	1.00	10	1.40	25.0	2.10	50.0	6.60			Gerberick et al. (2005)
Pentachlorophenol	87-86-5	DMSO	+	+	20	10	2.10	25.0	3.50	50.0	5.40							Gerberick et al. (2005)
Perillaldehyde	2111-75-3	AOO	+	+	4.0	0.5	1.20	1.0	1.10	2.5	0.90	5.0	4.30					Gerberick et al. (2005)
Phenyl benzoate	93-99-2	AOO	+	+	20	5	2.30	10	2.10	25	3.50							Gerberick et al. (2005)
Phenylacetaldehyde	127-78-1	AOO	+	+	3.0	1	0.70	2.5	1.80	5.0	7.80	10	8.80	25.0	19.00			Gerberick et al. (2005)
p-Methylhydro-cinnamic aldehyde	5406-12-2	AOO	+	+	14	2.5	1.20	5	1.40	10	2.60	25	4.2	50	10.7			Gerberick et al. (2005)
Potassium dichromate	7778-50-9	DMSO	+	+	0.08	0.025	1.60	0.05	1.40	0.1	3.80	0.25	5.30	0.5	16.10			Gerberick et al. (2005)
Propylene glycol	57-55-6	dH_2O	-	-	NC	50	1.20	100.0	1.60									Gerberick et al. (2005)
Propylparaben	94-13-3	AOO	-	-	NC	5	1.40	10	1.00	25.0	1.30							Gerberick et al. (2005)
p-tert-Butyl-a-ethyl-hydrocinnamal	80-54-6	AOO	+	+	19	1	1.3	2.5	2.5	10	2	25	3.7	50	9.3			Gerberick et al. (2005)
Pyridine	110-86-1	AOO	+	+	72	25	1.10	50.0	2.30	100.0	3.90							Gerberick et al. (2005)
R(+)-Limonene	5989-27-5	AOO	+	+	69	25	1.8	50	2.4	100	4							Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Saccharin	81-07-2	DMSO	-	-	NC	25	1.30	50.0	1.30	75.0	1.50							Gerberick et al. (2005)
Salicylic acid	69-72-7	AOO	-	-	NC	5	0.80	10	1.50	25.0	2.50							Gerberick et al. (2005)
Sodium lauroyl lactylate	13557-75-0	AOO	+	+	15	5	1.40	10.0	2.50	25.0	3.90							Gerberick et al. (2005)
Sodium lauryl sulfate	151-21-3	DMF	+	+	14	1	0.90	2.5	1.10	5.0	1.70	10.0	2.60	20.0	3.50			Gerberick et al. (2005)
Sodium-3,3,5-trimethyl-hexanoyloxy-benzenesulfonate	94612-91-6	DMSO	+	+	6.4	5	2.30	10.0	4.80	25.0	7.80							Gerberick et al. (2005)
Streptomycin sulfate	3810-74-0	DMF	-	-	NC	2.5	1.20	5.0	1.40	10	1.30	25.0	2.00	50.0	1.90			Gerberick et al. (2005)
Sulfanilamide	63-74-1	DMF	-	-	NC	10.0	1.00	25.0	1.00	50.0	0.90							Gerberick et al. (2005)
Sulfanilic acid	121-57-3	DMF	-	-	NC	5.0	1.50	10	1.90	25.0	2.20							Gerberick et al. (2005)
Tartaric acid	87-69-4	DMF	-	-	NC	5	1.00	10	0.90	25	1.50							Gerberick et al. (2005)
Tetramethyl thiuram disulfide	137-26-8	AOO	+	+	5.2	2.5	2.40	5.0	2.90	10	5.10							Gerberick et al. (2005)
trans-2-Decenal	3913-71-1	AOO	+	+	2.5	0.5	1.30	1	1.10	2.5	3.00	5	6	10	9.5			Gerberick et al. (2005)
trans-2-Hexenal	6728-26-3	AOO	+	+	5.5	0.5	1.2	1	1.2	2.5	2.3	5	2.6	10	6.4			Gerberick et al. (2005)
trans-Anethol	104-46-1	AOO	+	+	2.3	4.5	13.50	9	24.7	22.6	37.3							Gerberick et al. (2005)
Undec-10-enal	112-45-8	AOO	+	+	6.8	5.0	1.70	10	5.30	25.0	7.50	50.0	8.70	75.0	8.80			Gerberick et al. (2005)
Vanillin	121-33-5	AOO	-	-	NC	2.5	0.90	5.0	1.40	10	1.50	25.0	1.20	50.0	1.40			Gerberick et al. (2005)
Vinylidene dichloride	75-35-4	AOO	-	-	NC	10	0.80	25.0	0.80	50.0	0.90							Gerberick et al. (2005)
Vinylpyridine	1337-81-1	AOO	+	+	1.6	2.5	7.40	5.0	14.20	10	14.80							Gerberick et al. (2005)
(16-beta)-21-(Acetyloxy)-17-hydroxy-16-methylpregna-1,4,9(11)-triene-3,20-dione	910-99-6	DMF	-	-	NC	2.5	1.30	5	1.27	10	0.89							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
(1r)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl) methyl]isoquino-line [r-(r*,r*)]-2,3-bis(benzoyloxy)-butanedioate (1:1)	104832-01-1	DMF	-	-	NC	10	0.92	25	1.12	50	1.27							Glaxo SmithKline, Submitted by M.J. Olson
(2-Bromo-5-propoxyphenyl)(2-hydroxy-4-methoxyphenyl)-methadone	190965-45-8	ACE	-	-	NC	0.5	1.10	5	0.90	50	1.70							Glaxo SmithKline, Submitted by M.J. Olson
(2e)-2-[(2-Formyl-4-hydroxyphenyl)-methylidene]-butanedioic acid	773059-57-7	DMF	+	+	48	0.5	0.80	5	1.45	50	3.08							Glaxo SmithKline, Submitted by M.J. Olson
(2-Oxo-1-phenyl-pyrrolidin-3-yl)(triphenyl)-phosphonium bromide	148776-18-5	DMSO	-	-	NC	2.5	1.64	5	2.45	10	1.40							Glaxo SmithKline, Submitted by M.J. Olson
(2R,4S)-4-(4-Acetyl-1-piperazinyl)-n-{(1r)-1-[3,5-bis(trifluoro-methyl)phenyl]-ethyl}-2-(4-fluoro-2-methylphenyl)-n-methyl-1-piperidine-carboxamide monomethane-sulfonate	414910-30-8	DMF	-	-	NC	2.5	1.07	5	0.90	10	1.47							Glaxo SmithKline, Submitted by M.J. Olson
(2S,4S)-1-[(2s)-2-Amino-3,3-bis(4-fluorophenyl)-1-oxopropyl]-4-fluoro-2-pyrroli-dine carbonitrile	483369-58-0	DMSO	-	-	NC	5	0.99	10	1.60	25	2.44							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
(3as,4r,5s,6s,8r,9r,9ar,10r)-6-Ethenyldeca-hydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3ah-cyclopentacyclo-octen-8-yl [[(3-exo)-8-methyl-8-azabicyclo-[3.2.1]oct-3-yl]thio]-acetate	224452-66-8	AOO	-	-	NC	0.5	1.00	2	1.40	5	1.20							Glaxo SmithKline, Submitted by M.J. Olson
(3as,4r,5s,6s,8r,9r,9ar,10r)-6-Ethenyldeca-hydro-5-hydroxy-4,6,9,10-tetra-methyl-1-oxo-3a,9-propano-3ah-cyclopentacyclooct en-8-yl hydroxyacetate	125-65-5	DMF	-	-	NC	10	1.38	25	1.42	50	1.56							Glaxo SmithKline, Submitted by M.J. Olson
(3-Endo)-8-methyl-8-azabicyclo[3.2.1]-octan-3-ol	120-29-6	DMF	+	+	8.9	10	4.11	25	12.85	50	26.14							Glaxo SmithKline, Submitted by M.J. Olson
(3r,3as,6ar)-Hexahydrofuro-[2,3-b]furan-3-ol	156928-09-5	DMF	-	-	NC	1	0.78	3	0.91	10	0.95							Glaxo SmithKline, Submitted by M.J. Olson
(3r,3as,6ar)-Hexahydrofuro-[2,3-b]furan-3-yl [(1s,2r)-3-[(1,3-benzodioxol-5-ylsulfonyl)(2-methylpropyl)-amino]-2-hydroxy-1-[[4-[(2-methyl-4-thiazolyl)methoxy] phenyl]methyl]-propyl]carbamate	313682-08-5	DMF	-	-	NC	2.5	1.46	7.5	0.92	25	1.04							Glaxo SmithKline, Submitted by M.J. Olson
(3R6R)-3-(2,3-Dihydro-1h-inden-2-yl)-1-[(1r)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1s)-1-methylpropyl]-2,5-piperazinedione	820957-38-8	DMF	-	-	NC	5	0.74	10	1.41	25	1.62							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
(4r,5s)-(-)-1,5-Dimethyl-4-phenyl-2-imidazolidinone	92841-65-1	DMSO	-	-	NC	10	1.80	25	2.10	50	1.90							Glaxo SmithKline, Submitted by M.J. Olson
(4r,5s)-1,5-Dimethyl-3-(1-oxo-2-propenyl)-4-phenyl-2-imidazo-lidinone	139109-23-2	ACE	+	+	0.004	0.5	14.10	5	19.50	50	16.80							Glaxo SmithKline, Submitted by M.J. Olson
(4S)-1-(tert-Butoxycarbonyl)-4-fluoro-l-prolinamide	426844-22-6	DMF	-	-	NC	2.5	1.12	5	0.99	10	1.60							Glaxo SmithKline, Submitted by M.J. Olson
(4S)-1-(tert-Butoxycarbonyl)-4-fluoro-l-proline	203866-13-1	DMF	-	-	NC	5	0.88	10	0.82	25	1.29							Glaxo SmithKline, Submitted by M.J. Olson
(4S,5R)-1-[(1R,2R,3S)-3-(1,3-Benzodioxol-5-yl)-1-(2-benzyloxy-4-methoxyphenyl)-1-hydroxy-6-propoxy-2-indanoyl]-3,4-dimethyl-5-phenyl-2-imidazolidinone	190965-47-0	DMF	-	-	NC	0.5	0.78	5	1.14	10	1.39							Glaxo SmithKline, Submitted by M.J. Olson
(Alpha-r)-n-alpha-dimethyl-3,5-bis(trifluoro-methyl	334477-60-0	DMF	-	-	NC	10	1.32	25	1.41	50	1.63							Glaxo SmithKline, Submitted by M.J. Olson
(R,S)-3-Amino-2,3,4,5-tetrahydro-n-(1-methylethyl)-2,4-dioxo-n,5-diphenyl-1h-1,5-benzodiazepine-1-acetamide	184944-86-3	PG	-	-	NC	5	1.06	10	1.00	25	1.19							Glaxo SmithKline, Submitted by M.J. Olson
(s)-(-)-1-Phenylpropyl-amine	3789-59-1	AOO	-	-	NC	0.5	0.81	5	0.69	50	0.99							Glaxo SmithKline, Submitted by M.J. Olson
(S)-2-(4-Fluoro-2-methylphenyl)4-piperidinone (s)-alpha-hydroxybenzene-acetic acid salt	414910-13-7	DMF	-	-	NC	10	1.79	25	1.85	50	2.10							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
[3aS-(3aAlpha, 4beta,5alpha, 6alpha,8beta, 9alpha,9abeta, 10S*)]-6-Ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH-cyclopentacyclooct en-8-yl [(methylsulfonyl)-oxy]acetate	60924-38-1	DMF	-	-	NC	10	2.46	25	2.40	50	1.54							Glaxo SmithKline, Submitted by M.J. Olson
[4-(Ethoxymethyl)-2,6-dimethoxyphenyl]-boronic acid	591249-50-2	DMF	-	-	NC	10	0.87	25	0.58	50	1.00							Glaxo SmithKline, Submitted by M.J. Olson
[4S-[1(E),4Alpha, 5alpha]]-1-[3-[2-[4-Methoxy-2-(phenylmethoxy)-benzoyl]-4-propoxyphenyl]-1-oxo-2-propenyl]-3,4-dimethyl-5-phenyl-2-imidazoli-dinone	190965-46-9	DMF	-	-	NC	0.05	0.88	0.5	0.59	5	0.56							Glaxo SmithKline, Submitted by M.J. Olson
1-(4-Ethoxy-phenyl)-2-[4-(methyl-sulfonyl)phenyl]-ethanone	346413-00-1	DMSO	-	-	NC	1	1.82	2.5	2.34	5	1.89							Glaxo SmithKline, Submitted by M.J. Olson
1,1-Dimethylethyl [(1s)-1-[bis(4-fluorophenyl)-methyl]-2-[(2s,4s)-2-cyano-4-fluoro-1-pyrrolidinyl]-2-oxoethyl]carba-mate	483368-24-7	AOO	-	-	NC	10	0.97	25	0.81	50	0.99							Glaxo SmithKline, Submitted by M.J. Olson
1,1-Dimethylethyl [(1s)-2-[4-[(2-methyl-4-thiazolyl)methoxy] phenyl]-1-(2s)-oxiranylethyl]-carbamate	313680-92-1	DMF	-	-	NC	5	1.04	10	0.84	25	1.16							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
1,1-Dimethylethyl 3-[[[[(3s)-2,3,4,5-tetrahydro-1-[2-[(1-methylethyl)phenyl amino]-2-oxoethyl]-2,4-dioxo-5-phenyl-1h-1,5-benzodiazepin-3-yl]amino] carbonyl]amino] benzoate	305366-94-3	DMF	+	+	38	10	2.10	25	2.20	50	3.80							Glaxo SmithKline, Submitted by M.J. Olson
1,2,3,5,6,7-Hexahydro-2-thioxo-4h-cyclopentapyrimi-din-4-one	35563-27-0	PG	-	-	NC	5	0.63	10	1.71	25	1.37							Glaxo SmithKline, Submitted by M.J. Olson
1,3-Benzodioxazole-5-sulphonyl chloride	115010-10-1	AOO	+	+	0.4	10	13.54	25	16.56	50	16.76							Glaxo SmithKline, Submitted by M.J. Olson
1-[3-(Cyclopentyl-oxy)-4-methoxy-phenyl]-4-oxocyclohexane carbonitrile	152630-47-2	DMSO	-	-	NC	10	2.70	25	2.80	50	2.20							Glaxo SmithKline, Submitted by M.J. Olson
1-[5-[(4-Fluorophenyl)meth yl]-2-furanyl]ethanone	280571-34-8	AOO	-	-	NC	0.5	1.00	5	1.00	50	1.20							Glaxo SmithKline, Submitted by M.J. Olson
14-Hydroxynor-morphinone	84116-46-1	PG	+	+	8.4	5	1.20	10	3.88	25	6.24							Glaxo SmithKline, Submitted by M.J. Olson
2-(3,4-Dimethyl-phenyl)-5--methyl-2,4-dihydropyrazol-3-one	18048-64-1	DMF	+	+	IDR[3]	2.5	4.41	7.5	4.82	25	8.46							Glaxo SmithKline, Submitted by M.J. Olson
2-(4-Ethoxyphenyl)-3-[4-(methyl-sulfonyl)phenyl-]pyrazolo[1,5-b]-pyridazine	221148-46-5	DMF	-	-	NC	5	0.98	10	0.97	25	0.94							Glaxo SmithKline, Submitted by M.J. Olson
2-(4-Oxopentyl)-1h-isoindole-1,3(2h)-dione	3197-25-9	AOO	-	-	NC	0.25	0.58	2.5	1.54	25	0.67							Glaxo SmithKline, Submitted by M.J. Olson
2-(Benzyl)tert-butyl)amino)-1-(alpha,4-dihydroxy-m-tolyl)ethane	24085-03-8	DMF	-	-	NC	10	0.67	25	1.10	50	1.28							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
2,3,4,5-Tetrahydro-n-(1-methylethyl)-2,4-dioxo-n,5-diphenyl-3-[(phenylmethoxy)-imino]-1h-1,5-benzodiazepine-1-acetamide	305366-97-6	DMF	-	-	NC	5	1.18	10	1.76	25	1.67							Glaxo SmithKline, Submitted by M.J. Olson
2,3-Dimethyl-2h-indazol-6-amine	444731-72-0	DMF	-	-	NC	5	0.74	10	0.95	25	1.16							Glaxo SmithKline, Submitted by M.J. Olson
2,4-Dichloro-pyrimidine	3934-20-1	DMF	+	+	0.7	0.25	0.76	0.75	3.46	2.5	8.64							Glaxo SmithKline, Submitted by M.J. Olson
2,6-Dimethoxy-4-methyl-5-[3-(trifluoromethyl)-phenoxy]-8-quinolinamine	106635-86-3	AOO	-	-	NC	0.5	2.30	5	2.10	50	1.80							Glaxo SmithKline, Submitted by M.J. Olson
2,6-Dimethoxy-4-methyl-8-nitro-5-[3-(trifluoromethyl)-phenoxy]quinoline	189746-15-4	PG	+	+	3.5	3	2.90	10	4.29	30	5.34							Glaxo SmithKline, Submitted by M.J. Olson
2-[(Benzyloxy)-imino]malonic acid	305366-96-5	AOO	-	-	NC	10	1.17	25	1.88	50	2.40							Glaxo SmithKline, Submitted by M.J. Olson
2-[1-(4-Bromophenyl)-1-phenylethoxy]-n,n-dimethyl-ethanamine hydrochloride	13977-28-1	DMF	+	+	5.5	0.5	2.38	5	2.88	15	5.08							Glaxo SmithKline, Submitted by M.J. Olson
2-Amino-di-phenylamine	534-85-0	AOO	+	+	0.5	10	10.20	25	12.40	50	7.70							Glaxo SmithKline, Submitted by M.J. Olson
2-Aminoethyl-methylsulfone	49773-20-8	0.5% Tween 80 in H_2O	-	-	NC	10	0.40	25	0.30	50	0.30							Glaxo SmithKline, Submitted by M.J. Olson
2-Benzyl-tert-butylamino-3'-hydroxymethyl-4'-hydroxyaceto-phenone hydrochloride	24085-08-3	DMF	+	+	22	0.5	0.96	5	1.54	50	5.44							Glaxo SmithKline, Submitted by M.J. Olson
2-Bromo-5-hydroxy-benzaldehyde	2973-80-0	AOO	+	+	2.6	0.5	1.25	5	4.93	50	21.40							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
2-Bromo-5-propoxybenzoic acid	190965-43-6	ACE	-	-	NC	0.5	0.60	5	0.70	50	1.10							Glaxo SmithKline, Submitted by M.J. Olson
2-Chloro-6-methoxy-4-methylquinoline	6340-55-2	DMF	-	-	NC	0.1	1.07	1	0.98	10	1.11							Glaxo SmithKline, Submitted by M.J. Olson
2-chloro-1-[(3-fluorophenyl)-methoxy]-4-nitrobenzene	443882-99-3	AOO	+	+	IDR[3]	5	3.96	10	2.62	25	3.22							Glaxo SmithKline, Submitted by M.J. Olson
2-Nitro-4-(propylthio)benzen-amine	54393-89-4	AOO	Equiv	+	IDR[3]	0.5	1.97[4]	5	1.34[4]	15	8.00[5]							Glaxo SmithKline, Submitted by M.J. Olson
3,4-Dichloroaniline hydrochloride	95-76-1	DMF	+	+	18	0.25	1.02	2.5	1.75	25	3.53							Glaxo SmithKline, Submitted by M.J. Olson
3-[(2r)-3-[[2-(2,3-Dihydro-1h-inden-2-yl)-1,1-dimethyl-ethyl]amino]-2-hydroxypropoxy]-4,5-difluoro-benzene propanoic acid	753449-67-1	DMF	-	-	NC	5	0.71	15	1.02	50	1.28							Glaxo SmithKline, Submitted by M.J. Olson
3'-[(2z)-[1-(3,4-Dimethylphenyl)-1,5-dihydro-3-methyl)-5-oxo-4h-pyrazol-4-ylidene]hydrazino]-2'-hydroxy-[1,1'-biphenyl]-3-carboxylic acid, compound with 2-aminoethanol (2:1)	496775-62-3	AOO	-	-	NC	5	1.38	15	1.05	50	0.84							Glaxo SmithKline, Submitted by M.J. Olson
3-[4-[(6-Bromohexyl)oxy]-butyl]benzene-sulfonamide	452342-04-0	AOO	-	-	NC	10	1.02	25	0.82	50	0.68							Glaxo SmithKline, Submitted by M.J. Olson
3-Chloro-4-fluorobenzoyl chloride	65055-17-6	PG	+	+	7.8	3	2.24	10	3.36	30	8.99							Glaxo SmithKline, Submitted by M.J. Olson
3-Fluoro-5-(3-pyridinyl)benzen-amine	181633-36-3	DMSO	+	+	15	0.5	1.90	5	2.20	50	5.90							Glaxo SmithKline, Submitted by M.J. Olson
3-Hydroxy-2-phenyl-4-quinolinecarboxylic acid	485-89-2	DMSO	-	-	NC	0.05	0.56	0.5	0.79	5	1.04							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
3-Hydroxy-4-methoxy-benzaldehyde	621-59-0	DMF	-	-	NC	0.25	0.75	2.5	1.15	25	1.35							Glaxo SmithKline, Submitted by M.J. Olson
3-Propoxybenzoic acid	190965-42-5	ACE	-	-	NC	0.5	1.10	5	1.20	50	1.10							Glaxo SmithKline, Submitted by M.J. Olson
4-(Bromomethyl)-benzoic acid ethyl ester	26496-94-6	AOO	+	+	IDR[3]	0.5	11.73	5	12.87	50	ND[6]							Glaxo SmithKline, Submitted by M.J. Olson
4'-(Trifluoro-methyl)-[1,1'-biphenyl]-4-carboxaldehyde	90035-34-0	DMF	-	-	NC	1	1.36	3	1.55	10	2.58							Glaxo SmithKline, Submitted by M.J. Olson
4-[4-[[(3R)-1-Butyl-3-[(r)-cyclohexyl-hydroxymethyl]-2,5-dioxo-1,4,9-triazaspiro[5.5]-undec-9-yl]methyl]phenoxy] benzoic acid	461443-59-4	DMSO	-	-	NC	2.5	1.07	5	1.27	10	1.63							Glaxo SmithKline, Submitted by M.J. Olson
4-Amino-3-nitrophenyl thiocyanate	54029-45-7	DMSO	+	+	0.8	0.5	2.30	1	3.32	5	3.55							Glaxo SmithKline, Submitted by M.J. Olson
4-Bromo-1-phthalimidopentane	59353-62-7	ACE	+	+	27	0.5	1.00	5	1.10	50	4.20							Glaxo SmithKline, Submitted by M.J. Olson
4-Chloro-6-iodoquinazoline	98556-31-1	AOO	+	+	IDR[3]	5	11.30	10	9.30	25	17.30							Glaxo SmithKline, Submitted by M.J. Olson
4-Fluoro-2-pyrrolidine-carboxamide	748165-40-4	DMF	-	-	NC	10	1.22	25	1.15	50	1.03							Glaxo SmithKline, Submitted by M.J. Olson
4-Iodo-1-phthalimido-pentane	63460-47-9	ACE	+	+	5.0	0.5	1.70	5	3.00	50	9.50							Glaxo SmithKline, Submitted by M.J. Olson
5-[[4-[(2,3-Dimethyl-2h-indazol-6-yl)-methylamino]-2-pyrimidinyl]amino] -2-methylbenzene-sulfonamide	444731-52-6	AOO	-	-	NC	5	1.13	10	0.91	25	0.91							Glaxo SmithKline, Submitted by M.J. Olson
5-Amino-2-methylbenzene-sulfonamide	6973-09-7	DMF	-	-	NC	5	1.36	10	1.12	25	1.42							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
5-Chloro-2,6-dimethoxy-4-methyl-8-nitroquinoline	189746-21-2	DMSO	+	+	IDR[3]	0.5	8.00	5	7.00	10	7.50							Glaxo SmithKline, Submitted by M.J. Olson
5-Chloro-2,6-dimethoxy-4-methylquinoline	189746-19-8	DMSO	-	-	NC	0.5	0.90	5	0.70	25	1.00							Glaxo SmithKline, Submitted by M.J. Olson
5'-Chloro-2'-hydroxy-3'-nitro-[1,1'-biphenyl]-3-carboxylic acid	376592-58-4	DMF	+	+	20	5	1.37	15	2.83	50	3.96							Glaxo SmithKline, Submitted by M.J. Olson
5-Chloro-6-methoxy-4-methyl-8-nitro-2(1h)quinolinone	189746-23-4	PG	+	+	IDR[3]	2.5	10.82	5	9.86	10	10.72							Glaxo SmithKline, Submitted by M.J. Olson
5-Methoxy-2-nitro-4-(trifluoromethyl) benzene acetonitrile	178896-77-0	DMSO	-	-	NC	0.5	1.30	5	1.50	50	1.60							Glaxo SmithKline, Submitted by M.J. Olson
5-Methoxy-6-(trifluoromethyl)-2,3-dihydro-1h-indole	178896-79-2	DMSO	+	+	37	0.5	1.10	5	1.30	50	3.70							Glaxo SmithKline, Submitted by M.J. Olson
6-(Diethylamino)-1-hexanol	06947-12-2	PG	+	+	10	3	0.79	10	2.92	30	25.50							Glaxo SmithKline, Submitted by M.J. Olson
6-(Trifluoro-methyl)-2,3-dihydro-5-methyl-1h-indole, hydrochloride	280121-24-6	ETOH (100%)	-	-	NC	0.5	1.10	5	1.00	50	1.20							Glaxo SmithKline, Submitted by M.J. Olson
6-[(2-Methyl-3-pyridinyl)oxy]-3-pyridinamine	181633-42-1	DMSO	+	+	45	0.5	1.00	5	1.40	50	3.20							Glaxo SmithKline, Submitted by M.J. Olson
6-Chloro-1-hexanol	2009-83-8	AOO	-	-	NC	5	2.35	15	1.66	50	1.92							Glaxo SmithKline, Submitted by M.J. Olson
6-Diethylaminohexyl bromide hydrobromide	64993-14-2	PG	+	+	5.3	3	1.76	10	5.46	30	14.69							Glaxo SmithKline, Submitted by M.J. Olson
6-Iodo-quinazolin-4-ol	16064-08-7	DMF	-	-	NC	1	0.72	2.5	1.16	5	0.93							Glaxo SmithKline, Submitted by M.J. Olson
6-Methoxy-4-methyl-2(1H)-quinolinone	5342-23-4	PG	-	-	NC	3	1.21	10	1.49	30	1.32							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
7-[(4z)-3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethane-sulfonate	210353-53-0	DMSO	+	+	8.6	0.1	0.75	1	1.38	10	3.30							Glaxo SmithKline, Submitted by M.J. Olson
8-[(4-Phthalimido-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline	106635-87-4	PG	-	-	NC	3	2.22	10	1.50	30	1.49							Glaxo SmithKline, Submitted by M.J. Olson
8-Amino-6-methoxy-4-methylquinoline	57514-21-3	PG	-	-	NC	3	1.23	10	2.83	30	2.50							Glaxo SmithKline, Submitted by M.J. Olson
8-Chloro-3-pentyl-3,7-dihydro-1h-purine-2,6-dione	862892-90-8	DMF	+	+	32	5	2.00	15	0.85	50	5.29							Glaxo SmithKline, Submitted by M.J. Olson
8-Hydroxy-5-[(1r)-1-hydroxy-2-[[2-[4-[(6-methoxy[1,1'-biphenyl]-3-yl)amino]phenyl]-ethyl]amino]ethyl]-2(1h)-quinolinone	530084-87-8	DMF	-	-	NC	5	0.96	10	2.34	25	1.58							Glaxo SmithKline, Submitted by M.J. Olson
Adipic acid	124-04-9	DMSO	-	-	NC	10	1.01	25	0.93	50	0.79							Glaxo SmithKline, Submitted by M.J. Olson
Alpha-(p-toluenesulfonyl)-4-fluorobenzyliso-nitrile	165806-95-1	DMF	+	+	45	0.5	4.72	5	2.78	50	3.03							Glaxo SmithKline, Submitted by M.J. Olson
Anthranilic acid	118-92-3	AOO	-	-	NC	10	0.90	25	1.10	50	1.40							Glaxo SmithKline, Submitted by M.J. Olson
cis-4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl] cyclo-hexanecarboxylic acid	153259-65-5	DMSO	-	-	NC	0.5	1.16	5	1.27	10	1.28							Glaxo SmithKline, Submitted by M.J. Olson
Cytosine hemihydrate	71-30-7	PG	-	-	NC	5	0.40	10	0.90	25	0.70							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-pimelate	152630-48-3	AOO	-	-	NC	0.5	1.66	5	1.59	50	1.76							Glaxo SmithKline, Submitted by M.J. Olson
Dimethyl carbonate	616-38-6	AOO	-	-	NC	0.5	0.64	5	0.69	50	1.71							Glaxo SmithKline, Submitted by M.J. Olson
Endo-tropine-3-mesylate	35130-97-3	DMF	+	+	4.4	5	3.45	10	5.98	25	25.06							Glaxo SmithKline, Submitted by M.J. Olson
Ethyl (3-endo)-8-methyl-8-azabicyclo[3.2.1]-octane-3-acetate	56880-11-6	DMF	+	+	5.5	10	6.77	25	12.58	50	ND[6]							Glaxo SmithKline, Submitted by M.J. Olson
Ethyl (z)-alpha-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]-2-[(triphenylmethyl) amino]- 4-thiazoleacetate	68672-65-1	Buta-none	-	-	NC	2.5	0.80	5	1.32	10	0.92							Glaxo SmithKline, Submitted by M.J. Olson
Ethyl 1h-1,2,4-triazole-3-carboxylate	64922-04-9	DMF	-	-	NC	0.25	1.00	2.5	1.20	25	1.00							Glaxo SmithKline, Submitted by M.J. Olson
Ethyl 2,6-dichloro-5-fluoro-beta-oxo-3-pyridinepropanoate	96568-04-6	AOO	-	-	NC	0.25	0.59	2.5	1.33	25	1.97							Glaxo SmithKline, Submitted by M.J. Olson
Ethyl 4-iodobenzoate	51934-41-9	AOO	+	+	8.0	0.5	1.10	5	2.20	50	14.30							Glaxo SmithKline, Submitted by M.J. Olson
Isopropyl dicyandiamide	35695-36-4	DMF	-	-	NC	0.25	1.36	2.5	1.35	25	1.24							Glaxo SmithKline, Submitted by M.J. Olson
m-Chloropropio-phenone	34841-35-5	AOO	-	-	NC	10	0.86	25	0.73	50	1.25							Glaxo SmithKline, Submitted by M.J. Olson
Methyl 4-(bromomethyl) benzoate	2417-72-3	AOO	+	+	IDR[3]	0.5	26.83	5	18.47	50	ND[6]							Glaxo SmithKline, Submitted by M.J. Olson
n-(2-Chloro-4-pyrimidinyl)-2,3-drimethyl-2h-indazol-6-amine	444731-74-2	DMF	-	-	NC	1	0.80	2.5	0.74	5	1.07							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
n-(2-Chloro-4-pyrimidinyl)-n,2,3-trimethyl-2h-indazol-6-amine	444731-75-3	DMF	-	-	NC	1	1.28	2.5	1.47	5	2.15							Glaxo SmithKline, Submitted by M.J. Olson
n-(3,4-Dichlorophenyl)-n'-(1-methylethyl)-imidodicarbon-imidic diamide monohydrochloride	15537-76-5	DMF	+	+	1.3	0.25	1.64	2.5	4.61	25	ND[6]							Glaxo SmithKline, Submitted by M.J. Olson
n-(4-Methoxyphenyl)-3-oxobutanamide	5437-98-9	PG	+	+	2.2	3	3.10	10	3.49	30	10.33							Glaxo SmithKline, Submitted by M.J. Olson
n-[(1,1-Dimethylethoxy)-carbonyl]-l-tyrosine, ethyl ester	72594-77-5	AOO	-	-	NC	10	1.18	25	1.09	50	0.64							Glaxo SmithKline, Submitted by M.J. Olson
n-[(1-Butyl-4-piperidinyl)methyl]-3,4-dihydro-2h-[1,3]oxazino[3,2-a]indole-10-carboxamide	152811-62-6	AOO	-	-	NC	0.5	0.80	5	1.20	25	1.30							Glaxo SmithKline, Submitted by M.J. Olson
n-[2-(Diethylamino)ethyl]-2-[[(4-fluorophenyl)-methyl]thio]-4,5,6,7-tetrahydro-4-oxo-n-[[4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]-1h-cyclopentapyrim-idine-1-acetamide	356057-34-6	EtOH/ dH_2O (4:1)	+	+	11	5	1.11	10	2.43	25	12.71							Glaxo SmithKline, Submitted by M.J. Olson
n-[2-Benzyloxy-5-(2-bromo-1-hydroxy-ethyl)-phenyl]-formamide	201677-59-0	DMF	-	-	NC	10	0.98	25	0.68	50	0.97							Glaxo SmithKline, Submitted by M.J. Olson
n-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-fluoro-beta-(4-fluorophenyl)-l-phenylalanine	481055-29-2	DMF	-	-	NC	10	1.47	25	2.41	50	2.28							Glaxo SmithKline, Submitted by M.J. Olson
1-Aminopyridazin-ium iodide	35073-04-2	DMF	-	-	NC	10	1.17	25	1.43	50	1.25							Glaxo SmithKline, Submitted by M.J. Olson

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
n-Isopropyl-n-phenyl-2-(2-phenylamino-phenylamino)-acetamide	161455-90-9	DMF	+	+	2.1	2.5	3.80	5	7.30	10	6.60							Glaxo SmithKline, Submitted by M.J. Olson
Oripavine	467-04-9	DMF	+	+	8.6	2.5	1.90	5	2.50	10	3.20							Glaxo SmithKline, Submitted by M.J. Olson
Phenylmethyl 2-(4-fluoro-2-methylphenyl)-4-oxo-3,4-dihydro-1(2h)-pyridine-carboxylate	414909-98-1	DMF	-	-	NC	10	1.67	25	1.85	50	1.47							Glaxo SmithKline, Submitted by M.J. Olson
rel-(3r,3as,6ar)-Hexahydrofuro[2,3-b]furan-3-yl 4-nitrophenyl carbonate	252873-35-1	DMF	+	+	IDR[3]	2.5	3.48	7.5	3.40	25	3.54							Glaxo SmithKline, Submitted by M.J. Olson
Sodium ethyl xanthate	140-90-9	PG	+	+	7.3	5	1.57	10	4.70	25	9.42							Glaxo SmithKline, Submitted by M.J. Olson
tert-Butyl-3-aminobenzoate	92146-82-2	DMF	-	-	NC	10	1.24	25	1.02	50	1.08							Glaxo SmithKline, Submitted by M.J. Olson
Trienol	13504-15-9	DMF	-	-	NC	5	1.40	10	1.10	25	1.00							Glaxo SmithKline, Submitted by M.J. Olson
Veratraldehyde	120-14-9	AOO	+	+	3.2	0.5	2.63	5	3.24	50	3.47							Glaxo SmithKline, Submitted by M.J. Olson
Basil oil	8015-73-4	EtOH/ DEP (1:3)	+	+	IDR[3]	2.5	3.00	5.0	3.00	10.0	8.00	25.0	17.60	50.0	25.20			Lalko & Api (2006), Submitted by A. Api (RIFM)
Citral	5392-40-5	EtOH/ DEP (1:3)	+	+	6.3	2.5	2.80	5.0	2.30	10.0	5.10	25.0	11.40	50.0	22.10			Lalko & Api (2006), Submitted by A. Api (RIFM)
Citronella oil	8000-29-1	EtOH/ DEP (1:3)	-	-	NC	2.5	1.40	5.0	0.90	10.0	1.20	25.0	1.20	50.0	2.70			Lalko & Api (2006), Submitted by A. Api (RIFM)
Clove bud oil	8000-34-8	EtOH/ DEP (1:3)	+	+	7.1	1.0	1.10	2.5	1.80	5.0	2.50	10.0	3.70	25.0	5.90			Lalko & Api (2006), Submitted by A. Api (RIFM)
Clove leaf oil	8015-97-2	EtOH/ DEP (1:3)	+	+	8.0	2.5	1.60	5.0	1.50	10.0	4.00	25.0	9.50	50.0	11.40			Lalko & Api (2006), Submitted by A. Api (RIFM)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Clove stem oil	8015-98-3	EtOH/ DEP (1:3)	+	+	7.0	1.0	1.60	2.5	1.70	5.0	2.20	10.0	4.20	25.0	8.90			Lalko & Api (2006), Submitted by A. Api (RIFM)
Eugenol	97-53-0	EtOH/ DEP (1:3)	+	+	5.5	2.5	1.20	5.0	2.70	10.0	6.00	25.0	14.30	50.0	19.40			Lalko & Api (2006), Submitted by A. Api (RIFM)
Geraniol	106-24-1	EtOH/ DEP (1:3)	+	+	12	2.5	1.70	5.0	2.40	10.0	2.80	25.0	4.80	50.0	6.00			Lalko & Api (2006), Submitted by A. Api (RIFM)
Geranium oil	8000-46-2	EtOH/ DEP (1:3)	-	-	NC	2.5	1.20	5.0	0.70	10.0	1.70	25.0	1.80	50.0	2.80			Lalko & Api (2006), Submitted by A. Api (RIFM)
Jasmine absolute (Grandiflorum)	8022-96-6	EtOH/ DEP (1:3)	+	+	5.9	1.0	1.20	2.5	1.80	5.0	2.00	10.0	7.40	25.0	11.80			Lalko & Api (2006), Submitted by A. Api (RIFM)
Jasmine absolute (Sambac)	8022-96-6	EtOH/ DEP (1:3)	+	+	36	10	1.70	25.0	2.50	50.0	3.60	75.0	10.80	100.0	16.20			Lalko & Api (2006), Submitted by A. Api (RIFM)
Lemongrass oil	8007-02-1	EtOH/ DEP (1:3)	+	+	6.5	2.5	0.90	5.0	2.10	10.0	5.10	25.0	10.30	50.0	13.10			Lalko & Api (2006), Submitted by A. Api (RIFM)
Litsea cubeba oil	68855-99-2	EtOH/ DEP (1:3)	+	+	8.5	2.5	2.00	5.0	2.30	10.0	3.30	25.0	7.90	50.0	16.00			Lalko & Api (2006), Submitted by A. Api (RIFM)
Palmarosa oil	8014-19-5	EtOH/ DEP (1:3)	+	+	9.5	2.5	1.10	5.0	2.10	10.0	3.10	25.0	3.60	50.0	5.00			Lalko & Api (2006), Submitted by A. Api (RIFM)
Spearmint oil	68917-46-4	EtOH/ DEP (1:3)	+	+	8.2	0.5	1.20	1.0	1.10	2.5	1.20	5.0	1.90	10.0	3.60			Lalko & Api (2006), Submitted by A. Api (RIFM)
Ylang Ylang (Extra)	8006-81-3	EtOH/ DEP (1:3)	+	+	6.8	0.5	1.50	1.0	1.40	2.5	2.10	5.0	2.50	10.0	3.90			Lalko & Api (2006), Submitted by A. Api (RIFM)
Ylang Ylang (III)	8006-81-3	EtOH/ DEP (1:3)	-	-	NC	0.5	1.30	1.0	1.70	2.5	2.10	5.0	2.60	10.0	2.60			Lalko & Api (2006), Submitted by A. Api (RIFM)
(1R,4R)-4-Isopropenyl-1-methyl-2-methylene-cyclohexane		AOO	-	-	NC	1	1.30	5	1.80	10	1.20	15	2.30	25	2.90			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
(3S,6R)-3-isopropyl-6-methylcyclohexene	5113-93-9	AOO	-	-	NC	1	0.84	10	1.00	25	2.90							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
(4Z)-2-Methyl-6-methyleneoct-4-ene			-	-	NC	1	1.10	5	0.87	10	0.78	15	0.89	25	2.10			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
(5R)-5-Isopropenyl-2-methyl-1-methylene-2-cyclohexene		AOO	+	+	7.3	0.5	0.94	5	1.90	15	6.60							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
2,2-bis-[4-(2-hydroxy-3 methacryloxypropoxy)phenyl)]-propane	1565-94-2	AOO	+	+	45	35	2.00	75	5.90									LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
2,4-Diamino-phenoxyethanol HCl	66422-95-5	AOO	+	+	5.5	1	1.60	2,5	1.60	5	2.70	10	5.70	25	8.30			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
2,4-Hexadienal	142-83-6	AOO	+	+	3.5	0.5	0.90	1	1.50	2.5	2.20	5	4.20	10	14.80			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
3,4-epoxyclohexylethyl-cyclopoly-methylsiloxane		AOO	-	-	NC	50	1.20	100	1.20									LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
4,4-Dibromobenzil	35578-47-3	AOO	+	+	21	5	1.50	10	1.60	25	3.60	50	5.70					LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
4-Isopropyl-1-methylene-cyclohexane		AOO	-	-	NC	1	1.20	10	0.71	25	1.40							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
5-Methyl-2-phenyl-2-hexenal	21834-92-4	AOO	+	+	4.4	0.5	1.00	1.0	1.30	2.5	0.50	5	3.80	10	17.70			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
a-Phellandrene	99-83-2	AOO	+	+	5.4	1.0	1.10	10	5.00	25	28.00							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
a-Terpinene	99-86-5	AOO	+	+	8.9	1	1.1	5	1.5	10	3.40	15	8.90	25	23.00			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Bandrowski's base	20048-27-5	AOO	+	+	0.02	0.01	1.10	0.025	3.10	0.05	5.70	0.1	6.50	0.25	5.60			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
beta-Phenyl-cinnamaldehyde	1210-39-5	AOO	+	+	0.6	0.1	2.00	0.25	2.30	0.5	1.90	1	5.90	2.5	10.60			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Bis-3,4-epoxycyclohexyl-ethyl-phenyl-methylsilane (Ph-Sil)		AOO	+	+	16	25	3.70	35	4.20	50	7.90							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
b-Phellandrene	555-10-2	AOO	+	+	NC	1.0	1.10	10	4.80	20	23.00							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
b-Terpinene	99-84-3	AOO	-	-	NC	1	1.4	10	1.30	25	2.1							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Butyl acrylate	141-32-2	AOO	+	+	11	1	0.70	2.5	1.30	5	1.50	10	2.50	25	8.70			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Chlorothalonil	1897-45-6	DMF	+	+	0.004	0.003	2.10	0.01	9.40	0.03	13.80	0.1	18.40	0.3	27.20			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Ethyl hexyl acrylate	103-11-7	AOO	+	+	9.7	0.5	1.10	1	1.20	2.5	0.90	5	1.20	10	3.10			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Iodopropynyl butylcarbamate	87977-28-4	AOO	+	+	0.9	0.1	0.70	1	3.40	5	4.20	10	12.00					LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Linalool alcohol	78-70-6	AOO	-	-	NC	1	1.00	10	1.30	30	1.30							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Linalool aldehyde		AOO	+	+	9.5	1	1.20	5	2.00	15	4.20							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Methyl acrylate	96-33-3	AOO	+	+	20	1	0.80	2.5	0.80	5	1.30	10	1.60	25	3.80			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Methyl pyruvate	600-22-6	AOO	+	+	2.4	1.0	1.20	2.5	3.10	5.0	4.70	10	8.00					LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Methyl methacrylate	80-62-6	AOO	+	+	90	10	1.40	30	1.50	50	1.50	75	2.10	100	3.60			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Norbornene fluoroalcohol	305815-63-8	AOO	+	+	46	5.0	0.70	10	0.80	25.0	1.90	50	3.20	100	3.70			LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
R-Carvone	2244-16-8	AOO	+	+	13	6	1.30	12	2.60	20	6.20							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
R-Carvoxime	2051-55-0	AOO	+	+	0.6	0.1	2.10	1	3.70	5	8.10							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Trans-2-methyl-2-butenal	497-03-0	AOO	-	-	NC	10	1.50	25	1.00	50	1.80							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
1-Chloro-2-dinitrobenzene	97-00-7	AOO	+	+	0.1	0.01	1.17	0.025	1.12	0.05	1.93	0.10	1.95	0.25	7.10			NTP Study, Submitted by D. Germolec
5-Amino-O-Cresol	2835-95-2	AOO	+	+	7.7	2.5	1.45	5.00	2.77	10.00	3.19							NTP Study, Submitted by D. Germolec
Atrazine	1912-24-9	ACE	-	-	NC	10	1.29	20.00	1.38	30.00	0.76							NTP Study, Submitted by D. Germolec
Azithromycin	83905-01-5	ACE	-	+	IDR[3]	10	3.72	20.00	1.54	40.00	2.10							NTP Study, Submitted by D. Germolec

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Butyl acrylate	141-32-2	ACE	+	+	24	10	1.00	20.00	2.18	30.00	4.07							NTP Study, Submitted by D. Germolec
Clarithromycin	81103-11-9	ACE	-	-	NC	1	1.78	2.00	1.03	4.00	1.18							NTP Study, Submitted by D. Germolec
Dicyclohexylcarbodiimide	538-75-0	ACE	+	+	0.057	0.006	1.03	0.03	1.71	0.06	3.16							NTP Study, Submitted by D. Germolec
Ethyl acrylate	140-88-5	ACE	-	-	NC	10	0.89	20.00	1.19	30.00	0.91							NTP Study, Submitted by D. Germolec
Ethyl-2-(Hydroxymethyl)-1,3- Propanediol Triacrylate		ACE	+	+	0.13	0.3	1.00	0.10	1.52	0.15	4.13	0.30	4.59					NTP Study, Submitted by D. Germolec
Methyl salicylate	119-36-8	AOO	-	-	NC	1	0.86	2.50	1.19	5.00	1.16	10.00	1.41	20.00	1.72			NTP Study, Submitted by D. Germolec
Pentaerythritol Triacrylate	3524-68-3	ACE	-	-	NC	0.005	1.19	0.01	0.92	0.05	1.68	0.10	2.43					NTP Study, Submitted by D. Germolec
Potassium dichromate	7778-50-9	DMSO	+	+	0.2	0.025	1.21	0.05	1.84	0.10	2.22	0.25	3.39					NTP Study, Submitted by D. Germolec
Rifamycin SV	14897-39-3	AOO	-	-	NC	3	0.94	10.00	1.02	30.00	1.33							NTP Study, Submitted by D. Germolec
Sodium metasilicate	6834-92-0	EtOH (15%)	-	-	NC	2	0.87	4.00	1.40	6.00	1.29							NTP Study, Submitted by D. Germolec
Trimethylolpropane Triacrylate	15625-89-5	ACE	-	-	NC	0.05	0.96	0.10	0.87	0.25	1.62							NTP Study, Submitted by D. Germolec
2.4-Dinitrobenzene sulfonic acid	89-02-1	H_2O	+	+	15	1	1.70	10	1.50	20	4.40							Ryan et al. (2002)
2.4-Dinitrobenzene sulfonic acid	89-02-1	Pluronic L92	+	+	6.4	1	0.90	10	4.40	20	11.60							Ryan et al. (2002)
2.4-Dinitrobenzene sulfonic acid	89-02-1	DMF	+	+	0.8	1	4.00	10	16.30	20	18.50							Ryan et al. (2002)
2.4-Dinitrobenzene sulfonic acid	89-02-1	DMSO	+	+	2.0	1	1.70	10	13.70	20	16.10							Ryan et al. (2002)
Formaldehyde	50-00-0	H_2O	+	+	15	1	1.20	10	2.50	20	3.60							Ryan et al. (2002)
Formaldehyde	50-00-0	Pluronic L92	+	+	4.2	1	2.00	10	4.80	20	8.80							Ryan et al. (2002)
Formaldehyde	50-00-0	DMF	+	+	0.3	1	6.70	10	13.20	20	17.70							Ryan et al. (2002)
Formaldehyde	50-00-0	DMSO	+	+	0.3	1	7.50	10	16.00	20	17.60							Ryan et al. (2002)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	6 Conc. (%)	6 SI	Data Source
Nickel sulfate	7786-81-4	Pluronic L92 (1%)	-	+	2.5	0.25	2.00	0.5	2.40	1	2.80	2.5	3.00	5	2.30			Ryan et al. (2002)
Nickel sulfate	7786-81-4	DMF	-	-	NC	0.25	0.90	0.5	1.10	1	1.60	2.5	1.60	5	2.20			Ryan et al. (2002)
Nickel sulfate	7786-81-4	DMSO	+	+	4.8	0.25	1.30	0.5	1.40	1	1.40	2.5	1.80	5	3.10			Ryan et al. (2002)
Pluronic L92®		H_2O	-	-	NC	1	1.30	2.5	1.00	5	1.00	10	0.80	25	0.80	50	2	Ryan et al. (2002)
Potassium dichromate	7778-50-9	Pluronic L92 (1%)	+	+	0.2	0.025	1.10	0.05	1.10	0.1	1.40	0.25	4.90	0.5	5.40			Ryan et al. (2002)
Potassium dichromate	7778-50-9	DMF	+	+	0.03	0.025	2.90	0.05	4.30	0.1	9.10	0.25	15.10	0.5	22.60			Ryan et al. (2002)
Potassium dichromate	7778-50-9	DMSO	+	+	0.05	0.025	1.40	0.05	2.50	0.1	9.50	0.25	25.90	0.5	10.10			Ryan et al. (2002)

Abbreviations: ACE = acetone; AOO = acetone: olive oil (4:1 by volume); BGIA = Berufsgenossenschaftliches Institut fur Arbeitsschutz (German Institute for Occupational Safety and Health); CASRN = Chemical Abstract Service Registry Number; CESIO = Comite Europeen des Agents de Surface et de Leurs Intermediaires Organiques (European Committee of Surfactants and their Organic Intermediates; Conc. = concentration; DBP = dibutyl phosphate; DEP = diethyl phthalate; dH2O = distilled water; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; ECPA = European Crop Protection Association; EFfCI = European Federation for Cosmetic Ingredients; ECPA = European Crop Protection Association; EtOH = ethanol; H_2O = water; LLNA = Local Lymph Node Assay; MEK = methyl ethyl ketone; NC = not calculated because no SI value was ≥ 3 (i.e., substance was a nonsensitizer); ND = no data; NTP = National Toxicology Program; PA/ H_2O = pluronic acid/ H_2O (1%); PG = propylene glycol; rLLNA = Reduced Local Lymph Node Assay; RIFM = Research Institute for Fragrance Materials; SI = stimulation index; Trad. = traditional

[1] "+" = Sensitizer; "-" = Non-sensitizer

[2] EC3 represents the estimated concentration needed to produce a stimulation index of three (i.e., a three fold increase in lymphocyte proliferation is observed for the test substance versus the vehicle control substance) and was calculated using the methods described in Ryan et al. (2007).

[3] IDR indicates an insufficient dose response to calculate an EC3 value using the methods in Ryan et al. (2007)

[4] Result of initial study

[5] Result of second study

[6] Data not obtained due to toxicity

Annex IV

Substances in the NICEATM LLNA Database for which an Initial Dose of 10% or Greater Elicited a Negative Result but a Subsequent Higher Dose Elicited a Positive Response

[This Page Intentionally Left Blank]

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	Data Source
1-(2',5' Dimethylphenyl)butane-1,3-dione	56290-55-2	ACE	+	+	12.5	10	2.30	20	5.10	40	9.50					Gerberick et al. (2005)
1,1-Dimethylethyl 3-[[[[(3s)-2,3,4,5-tetrahydro-1-[2-[(1-methylethyl)phenylamino]-2-oxoethyl]-2,4-dioxo-5-phenyl-1h-1,5-benzodiazepin-3-yl]amino]carbonyl]amino]-benzoate	305366-94-3	DMF	+	+	37.5	10	2.10	25	2.20	50	3.80					Glaxo SmithKline, Submitted by M.J. Olson
1-Chlorooctadecane	3386-33-2	AOO	+	+	16.3	10	1.70	25	4.80	50	7.30					Gerberick et al. (2005)
1-Chlorotetradecane	2425-54-9	AOO	+	+	20.2	10	1.10	25	3.90	50	6.30					Gerberick et al. (2005)
1-Iodohexadecane	544-77-4	AOO	+	+	19.1	10	1.60	25	3.90	50	6.40					Gerberick et al. (2005)
1-Iodononane	4282-42-2	AOO	+	+	24.2	10	1.30	25	3.10	50	4.60					Gerberick et al. (2005)
1-Iodotetradecane	19218-94-1	AOO	+	+	13.8	10	1.70	25	6.90	50	9.70					Gerberick et al. (2005)
1-Phenyl-2-methylbutane-1,3-dione	6668-24-2	ACE	+	+	29.1	10	1.70	20	2.00	40	4.20					Gerberick et al. (2005)
1-Phenyloctane--1,3-dione	55846-68-1	ACE	+	+	10.5	10	2.80	20	6.60	40	8.70					Gerberick et al. (2005)
2-(4-tert-Amylcyclohexyl)acetaldehyde	620159-84-4	AOO	+	+	36.8	25	2.10	50	4.00	100	9.10					Gerberick et al. (2005)
2,2,6,6-Tetramethyl-heptane-3,5-dione	1118-71-4	ACE	+	+	26.7	10	2.10	20	2.80	40	3.40					Gerberick et al. (2005)
2,2-bis-[4-(2-hydroxy-3 methacryloxypropoxy)phenyl)] -propane	1565-94-2	AOO	+	+	45.3	35	2.00	75	5.90							LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
3-Ethoxy-1-(2',3',4',5'-tetramethylphenyl)propane-1,3-dione	170928-69-5	ACE	+	+	33.0	10	1.10	20	1.70	40	3.70					Gerberick et al. (2005)
3-Methyleugenol	186743-26-0	AOO	+	+	31.6	11	1.50	27	2.30	54	6.40					Gerberick et al. (2005)
4,4,4-Trifluoro-1-phenylbutane-1,3-dione	362-06-7	ACE	+	+	20.0	10	2.10	20	3.00	40	4.60					Gerberick et al. (2005)
4-Allylanisole	140-67-0	AOO	+	+	17.7	10	1.20	25	4.70	50	4.50	100	8.00			Gerberick et al. (2005)
5-Methyl-2,3-hexanedione	13706-86-0	AOO	+	+	25.8	25	2.90	50	6.00	100	14.30					Gerberick et al. (2005)
5-Methyleugenol	186743-25-9	AOO	+	+	13.2	11	2.70	27	4.90	54	4.30					Gerberick et al. (2005)

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	Data Source
6-Methyleugenol	186743-24-8	AOO	+	+	16.9	11	1.90	27	4.90	54	8.30					Gerberick et al. (2005)
Atrazine SC	1912-24-9	Pluronic L92 (1%)	+	+	31.3	13	1.80	25	2.80	50	3.60	75	7.10	100	7.30	ECPA LLNA Project Report, Submitted by P. Botham
Butyl acrylate	141-32-2	ACE	+	+	24.4	10	1.00	20	2.18	30	4.07					NTP Study, Submitted by D. Germolec
Butyl glycidyl ether	2426-08-6	AOO	+	+	30.9	10	1.40	25	2.20	50	5.60					Gerberick et al. (2005)
C15-azlactone	176665-09-1	AOO	+	+	17.8	10	1.80	25	4.10	50	7.50					Gerberick et al. (2005)
C17-azlactone	176665-11-5	AOO	+	+	19.0	11	1.70	27	4.30	54	4.60					Gerberick et al. (2005)
C19-azlactone		AOO	-	+	26.4	12	2.50	29	3.10	59	2.50					Gerberick et al. (2005)
Cinnamic alcohol	104-54-1	AOO	+	+	20.6	10	1.80	25	3.50	50	3.90	90	5.70			Gerberick et al. (2005)
cis-6-Nonenal	2277-19-2	AOO	+	+	22.4	10	1.60	25	3.30	50	4.50	100	13.70			Gerberick et al. (2005)
Diethylacetaldehyde	97-96-1	AOO	+	+	76.1	25	1.20	50	0.80	75	2.40	100	16.30			Gerberick et al. (2005)
Dimethyl sulfoxide	67-68-5	AOO	+	+	71.9	25	2.70	50	2.30	100	3.90					Gerberick et al. (2005)
Ethyl acrylate	140-88-5	AOO	+	+	28.3	10	1.20	25	2.70	50	5.00					Gerberick et al. (2005)
Ethylene glycol dimethacrylate	97-90-5	MEK	+	+	28.3	10	1.20	25	2.40	50	7.00					Gerberick et al. (2005)
EXP 11120 A		Pluronic acid/H_2O (1%)	+	+	64.9	10	0.96	25	0.66	50	1.60	100	6.30			Bayer CropScience SA Studies, Submitted by E. Debruyne
FAR01060-00		Pluronic acid/H_2O (1%)	+	+	88.5	10	0.40	25	0.80	50	1.00	100	3.60			Bayer CropScience SA Studies, Submitted by E. Debruyne
Imidazolidinyl urea	39236-46-9	DMF	+	+	23.9	10	1.70	25	3.10	50	5.50					Gerberick et al. (2005)
Isopropyl myristate	110-27-0	AOO	+	+	43.8	25	2.10	50	3.30	100	3.40					Gerberick et al. (2005)
Jasmine absolute (Sambac)	8022-96-6	EtOH/DEP (1:3)	+	+	36.4	10	1.70	25	2.50	50	3.60	75	10.80	100	16.20	Lalko & Api (2006), Submitted by A. Api (RIFM)
Linalool alcohol	78-70-6	AOO	+	+	30.4	25	2.50	50	4.80	100	8.30					Gerberick et al. (2005)
Linoleic acid	60-33-3	AOO	+	+	14.1	10	1.50	25	7.00	50	9.10					EFfCI study, Submitted by P. Ungeheuer

Substance Name	CASRN	Vehicle	rLLNA[1]	Trad. LLNA[1]	EC3[2]	1 Conc. (%)	1 SI	2 Conc. (%)	2 SI	3 Conc. (%)	3 SI	4 Conc. (%)	4 SI	5 Conc. (%)	5 SI	Data Source
Methyl methacrylate	80-62-6	AOO	+	+	90.0	10	1.40	30	1.50	50	1.50	75	2.10	100	3.60	LLNA/EC3 Validation Study, Submitted by D. Basketter, I. Kimber, and F. Gerberick
Non-ionic surfactant 1		AOO	+	+	27.5	25	2.80	50	4.80	100	6.50					CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 2		AOO	-	+	47.1	25	1.50	50	3.20	100	2.90					CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 5		AOO	+	+	37.5	25	2.70	50	3.30	100	3.20					CESIO Report, Submitted by K. Skirda
Non-ionic surfactant 6		AOO	+	+	34.4	25	2.70	50	3.50	100	6.50					CESIO Report, Submitted by K. Skirda
Oleic acid	112-80-1	AOO	+	+	10.5	10	2.60	25	14.90	50	6.90					EFfCI study, Submitted by P. Ungeheuer
Pentachlorophenol	87-86-5	DMSO	+	+	19.6	10	2.10	25	3.50	50	5.40					Gerberick et al. (2005)
Precursor surfactant 1		AOO	+	+	60.7	25	2.20	50	2.70	100	4.10					CESIO Report, Submitted by K. Skirda
Pyridine	110-86-1	AOO	+	+	71.9	25	1.10	50	2.30	100	3.90					Gerberick et al. (2005)
Quinoxyfen/cyproconazole	124495-18-7/ 113096-99-4	Pluronic L92 (1%)	+	+	27.8	13	2.00	25	2.30	50	8.60	75	15.80	100	30.10	ECPA LLNA Project Report, Submitted by P. Botham
R(+)-Limonene	5989-27-5	AOO	+	+	68.8	25	1.80	50	2.40	100	4.00					Gerberick et al. (2005)
Undecylenic acid	112-38-9	AOO	+	+	19.4	10	2.50	25	3.30	50	4.40					EFfCI study, Submitted by P. Ungeheuer
Unsaturated fatty acid ester		AOO	+	+	27.1	25	2.80	50	5.20	100	4.70					CESIO Report, Submitted by K. Skirda

Abbreviations: ACE = acetone; AOO = Acetone: olive oil (4:1 by volume); CASRN = Chemical Abstract Services Registry Number; CESIO = Comite Europeen des Agents de Surface et de Leurs Intermediaires Organiques (European Committee of Surfactants and their Organic Intermediates; Conc. = concentration; DEP = diethyl phthalate; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; EFfCI = European Federation for Cosmetic Ingredients; ECPA = European Crop Protection Association; EtOH = ethanol; H2O = water; LLNA = Local Lymph Node Assay; MEK = methyl ethyl ketone; NTP = National Toxicology Program; rLLNA = Reduced Local Lymph Node Assay; RIFM = Research Institute for Fragrance Materials; SI = stimulation Index; Trad. = traditional

[1] "+" = Sensitizer; "-" = Non-sensitizer

[2] EC3 represents the estimated concentration needed to produce a stimulation index of three (i.e., a three-fold increase in lymphocyte proliferation is observed for the test substance versus the vehicle control substance).