COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT WITH THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

This Cooperative Research and Development Agreement (ACRADA@ or "Agreement") is entered into by and between **L'OREAL,** a French Corporation which has its principal place of business at 14 rue Royale, 75008 PARIS, FRANCE ("the Cooperator"), and the **National Center for Computational Toxicology** ("the Center"), of the **U.S. Environmental Protection Agency** ("EPA") under the authority of Title 15, United States Code ' ' 3710a-3710d (commonly known as the Federal Technology Transfer Act of 1986).

WITNESSETH:

A. WHEREAS, the Congress, in enacting the Federal Technology Transfer Act of 1986 (the "FTTA"), has found that Federal laboratories' developments should be made accessible to private industry, state and local governments, and has declared that one of the purposes of such Act is to improve the economic, environmental and social well being of the United States by stimulating the utilization of Federally-funded technology developments by such parties;

B. WHEREAS, the FTTA provides each Federal agency with the authority to permit the Directors of Government-operated laboratories to enter into cooperative research and development agreements with Federal or non-Federal entities, including private firms and organizations for the purpose of providing to, or obtaining from, collaborating parties, personnel, services, property, facilities, equipment, intellectual property or other resources toward the conduct of specified research and development efforts, which may include the disposition of patent or other intellectual property rights in the inventions resulting from such collaboration;

C. WHEREAS, the Center has performed and has sponsored substantial research and development with respect to computational and predictive toxicology;

D. WHEREAS, the Center possesses certain advanced scientific skills, facilities, special equipment, information, computer software, and know-how pertaining to computational and predictive toxicology relative to the ToxCast^{TM} reasearch program;

E. WHEREAS, the Cooperator possesses certain expertise in metabolism, genotoxicity, (Q)SAR modeling and integrated testing strategy (ITS) elaboration.

F. **WHEREAS**, the Center and the Cooperator are interested in the further research and development of the ToxCast™ project, especially in the areas of metabolism, genotoxicity, (Q)SAR modeling and ITS building, and its utilization by private and public entities;

G. **WHEREAS**, the Cooperator desires to provide resources for the Center's development and/or evaluation of the ToxCast™ project; and

H. **WHEREAS**, the Center views its collaboration with the Cooperator to develop/evaluate the ToxCast™ predicative toxicology technology to be in the furtherance of the public interest.

NOW, THEREFORE, the parties hereto agree as follows:

Article 1. Definitions

As used in this CRADA, the following terms shall have the following meanings and such meanings should be equally applicable to both the singular and plural forms of the terms defined:

1.1 **"CRADA" or "Agreement"** means this Cooperative Research and Development Agreement entered into by the Center pursuant to 15 U.S.C. ' 3710a.

1.2 **"Computer Software"** means computer software, computer programs, computer data bases, and documentation thereof developed, in whole or in part, under this Agreement.

1.3 **"Government"** means the Government of the United States of America.

1.4 **"Invention"** means any invention or discovery which is or may be patentable or otherwise protectable under the intellectual property laws of this or any foreign country.

1.5 **"Made"** in relation to any Invention means the conception or first actual reduction to practice of such Invention.

1.6 **"Proprietary Information"** means information which embodies trade secrets developed at private expense, or which is confidential scientific, business or financial information, provided that such information:

(a) Is not generally known or available from other sources without obligation concerning its confidentiality;

(b) Has not been made available by the owners to others without obligation concerning its confidentiality; and

(c) Is not already available to the Government without obligation concerning its confidentiality.

1.7 "Subject Data" means all recorded information first produced in the performance of this Agreement. This term includes Computer Software.

1.8 "Subject Invention" means any Invention conceived or first actually reduced to practice in the performance of work under this Agreement.

1.9 "Technology" means development of the ToxCast^{TM} predicative toxicology project, especially in the areas of metabolism, genotoxicity, (Q)SAR modeling and integrated testing strategies.

1.10 AWorks@ means any Computer Software or subject matter that is copyrightable.

Article 2. Cooperative Research

2.1 Statement of Work. Cooperative research and development work performed under this Agreement shall be performed in accordance with the Statement of Work ("SOW") attached hereto as Attachment A. The SOW sets forth a "period of performance." The Center and the Cooperator agree to perform the cooperative research and development work and to utilize such personnel, resources, facilities, equipment, skills, know-how and information as are reasonably necessary.

2.2 Review of Work. Periodic conferences shall be held between Center and Cooperator personnel for the purpose of reviewing the progress of the work to be accomplished under this Agreement. The Center shall have exclusive control and supervision over the conduct of all cooperative research and development work conducted at the Center facilities. The Cooperator shall have exclusive control and supervision over the conduct of all cooperative research and development work conducted at Cooperator facilities. It is understood that the nature of this cooperative research and development work is such that completion within the period of performance specified in the SOW or within the limits of financial support allocated, cannot necessarily be guaranteed. Accordingly, it is agreed that all cooperative research is to be performed on a best efforts basis.

2.3 Assigned Personnel. Each party to this Agreement shall perform its respective obligations under this Agreement under the direction of a "Project Manager" and a "Principal Investigator." Project Managers shall be responsible for the overall direction of the work, establishing budgets and providing such approvals and consents as are required hereunder. Principal Investigators shall be responsible for the scientific and technical conduct of the work, including the exchange of Subject Data and other information. The parties designate the following individuals as their respective representatives:

	Center	Cooperator
Project Manager	David Dix	Jean-Roch Meunier
Principal Investigator	Keith Houck	Gladys Ouédraogo

2.4 Scope Change. If at any time the Project Managers determine that the research data justify a substantial change in the direction of the work, the parties shall make a good faith effort to agree on any necessary changes to the SOW.

Article 3. Reports

3.1 Final Report. The Center shall submit a final report to the Cooperator of the Center's results within 90 calendar days after (a) completing the SOW or (b) the termination of this Agreement. The Cooperator shall submit a final report to the Center of the Cooperator's results within 90 calendar days after (a) completing the SOW or (b) the termination of this Agreement.

Article 4. Financial Obligations

4.1 Transfer of Funds. The Cooperator agrees to pay $100,000 ~~to 400,000.00~~ $200,000 to EPA for the performance of research specified in Article 2 and the SOW in Attachment A. A check payable to the U.S Environmental Protection Agency (EPA) must be delivered to EPA before work can be initiated by the Center. The check shall be mailed to:

U.S. Environmental Protection Agency
Cincinnati Financial Management Center
~~Attention: FTTA~~ FOIA and Misc. Payments
P.O. Box ~~371099M~~ 979078
~~Pittsburgh, PA 15251~~ St. Louis, MO 63197-9000

The check shall be accompanied by a copy of the first page of this Agreement, the signature page of this Agreement, and the SOW in Attachment A.

4.2 Assignment of Personnel. In addition to the funding by the Cooperator provided for in paragraph 4.1 above, the Cooperator shall provide the services of a qualified research associate who will assist in the efforts under the SOW in Appendix A. The associate shall be an employee of the Cooperator and shall be stationed at L'OREAL, 1 avenue Eugène Schueller, 93601 Aulnay-sous-bois, FRANCE.

4.3 Accounting Records. The Center shall maintain separate and distinct current accounts, records, and other evidence supporting all its expenditures of the Cooperator's cash contributions under this Agreement. The accounts and records shall be available for reasonable inspection and copying by the Cooperator or its authorized representative.

Article 5. Invention, Computer Software, and Patent Rights

5.1 The Center and the Cooperator believe that no Subject Inventions or Computer Software will be created during the work specified in this Agreement. Should it appear that any activity of this Agreement might involve the creation of Subject Inventions or Computer Software, the Center and the Cooperator will negotiate in good faith an amendment to this Agreement. The amendment will assign responsibilities for obtaining patents or other intellectual property rights pertaining to the Subject Inventions or Computer Software and will provide for appropriate allocation of any patent or intellectual property rights resulting from those Subject Inventions or Computer Software.

Article 6. Data and Publication

6.1 Proprietary Information. The Cooperator shall place a proprietary notice on all information it delivers to the Center under this Agreement which it asserts is Proprietary Information of the Cooperator The Center agrees that: 1) any information designated as Proprietary Information which is furnished by the Cooperator to the Center under this Agreement; 2) any information obtained by either party during the performance of this CRADA that would be claimed as Proprietary Information had it been submitted by the Cooperator; or 3) any information furnished by the Cooperator in contemplation of this Agreement; shall be treated as Proprietary Information and will be used by the Center only for the purpose of carrying out this Agreement or for Government purposes. Information designated as Proprietary Information shall not be disclosed, copied, reproduced or otherwise made available in any form whatsoever to any other person, firm, corporation, partnership, association or other entity without consent of the Cooperator except as such information may be subject to disclosure under the Freedom of Information Act (5 U.S.C. ' 552), and EPA's regulations at 40 C.F.R. Part 2, or as required to be disclosed by other statutes. The Center agrees to use its best efforts to protect the information designated as Proprietary Information from unauthorized disclosure. The Cooperator agrees that the Center is not liable for the disclosure of Proprietary Information which, after notice to and consultation with the Cooperator, EPA determines may not lawfully be withheld or which a court of competent jurisdiction requires to be disclosed. If no claim of confidentiality accompanies information at the time of submittal and a reasonable person would not have reason to believe such information was proprietary or of a confidential nature, then the information may be made public with no further notice to the Cooperator.

6.2 Release Restrictions. The Center shall have the right to use all Subject Data for any Governmental purpose; provided, however, that the Center shall not release such Subject Data

publicly or provide such Subject Data to any Government regulatory body or agency other than the EPA except:

(a) the Center in reporting the results of cooperative research may publish Subject Data, subject to the provisions of paragraph 6.3 below, upon agreement of the Cooperator and provided the Cooperator is given 45 days to review the manuscript and provide suggestions before publication; and

(b) the Center may release such Subject Data where such release is required pursuant to a request under the Freedom of Information Act (5 U.S.C. ' 552) and the EPA regulations at 40 C.F.R. Part 2 or as required to be disclosed by other statutes.

(c) The Cooperator agrees to not release any Subject Data without obtaining prior written consent from the Center.

(d) Pursuant to 35 U.S.C. ' 205, neither the Center nor the Cooperator shall release to the public any Subject Data or other data that discloses or enables an invention if a patent application is to be filed, until the party having the right to file a patent application or provisional patent application has had a reasonable time to file.

6.3 Publication. The Center and the Cooperator agree to confer and consult prior to the publication of Subject Data to ensure that no Proprietary Information is released and that patent rights are not jeopardized. Prior to submitting a manuscript for outside review which contains the results of the research under this Agreement, or prior to publication if no such review is made, each party shall be offered at least 45 calendar days to review such proposed publication and to file patent applications in a timely manner, if it is so entitled or required under this Agreement.

Article 7. Representations and Warranties

7.1 Representation and Warranties of the Center. The Center hereby represents and warrants to the Cooperator as follows:

7.1.1 Organization. The Center is a Federal center of the EPA and is wholly owned by the Government. The Center's substantial purpose is the performance of research or development.

7.1.2 Mission. The performance of the activities specified by this Agreement is consistent with the mission of the Center.

7.1.3 Authority. All prior reviews and approvals required by Federal regulations and laws have been obtained by the Center prior to the execution of this Agreement. The Center official executing this Agreement has the requisite authority to do so.

7.2 Representations and Warranties of the Cooperator. The Cooperator hereby represents and warrants to the Center as follows:

7.2.1 Corporate Organization. The Cooperator, as of the date hereof, is a corporation duly organized, validly existing and in good standing under the laws of the State of France.

7.2.2 Power and Authority. The Cooperator has the requisite power and authority to enter into this Agreement and to perform according to the terms thereof.

7.2.3 Due Authorization. The Board of Directors and stockholders of the Cooperator have taken all actions, if any, required to be taken by law, the Cooperator's Certificate or Articles of Incorporation, its bylaws or otherwise, to authorize the execution and delivery of this Agreement.

7.2.4 No Violation. The execution and delivery of this Agreement do not contravene any material provision of, or constitute a material default under, any material agreement binding on the Cooperator or any valid order of any court, or any regulatory agency or other body having authority to which the Cooperator is subject, nor, to the best of its knowledge, is the Cooperator the subject of any adversarial proceeding by any regulatory governmental agency.

Article 8. Termination

8.1 Termination by Mutual Consent. The Center and the Cooperator may elect to terminate this Agreement, or portions thereof, at any time by mutual consent. In such event the parties shall specify the disposition of all property, patents, unexpended or unobligated funds, and the results arising from the work completed or in progress under this Agreement. Upon termination by mutual consent, the Center, as of the termination date, shall make no new commitments, and as soon after the termination date as feasible, shall cancel all outstanding commitments that relate to those portions of this Agreement that have been mutually terminated.

8.2 Termination by Unilateral Action. Either party may unilaterally terminate this entire Agreement at the end of each step as described in the SOW in Attachment A by giving the other party written notice not more than thirty (30) calendar days after the end of each step. The Center shall make no new commitments after receipt of a written termination notice from the Cooperator and shall to the extent possible, by the termination date, cancel all outstanding commitments and contracts that were entered into as a consequence of the requirements of the SOW in Attachment A. However, the Center may, at its own expense, continue said commitments beyond said termination date without liability on the part of the Cooperator.

8.3 Termination Costs. Each party shall pay its own termination costs out of its own funds. Any funds furnished by the Cooperator which are unexpended or unobligated as of the date of termination will be returned to the Cooperator. In no event shall either party be liable for the direct and indirect termination costs of the other party or said other party's expenses caused by or related to the termination.

8.4 Survival. To the extent rights and obligations hereunder have accrued as of the date of expiration or termination, the following Articles of this Agreement shall survive any expiration or termination hereof: 5, 6, and 10, and any expiration or termination hereof shall not affect any license granted hereunder.

Article 9. Disputes

9.1 Settlement. Any dispute arising under this Agreement which cannot be readily resolved shall be submitted jointly to the signatories of this Agreement. A joint decision of the signatories or their designees shall be the disposition of such dispute. If the signatories are unable to jointly resolve a dispute within a reasonable period of time after submission of the dispute for resolution, the matter shall be submitted to the Administrator of EPA or the Administrator's designee for resolution.

9.2 Continuation of Work. Pending the resolution of any dispute or claim pursuant to this Article, the parties agree that performance of all obligations shall be pursued diligently in accordance with the direction of the Center signatory.

Article 10. Liability

10.1 EPA. EPA's responsibility for the payment of claims to the Cooperator or its employees for loss of property, personal injury or death caused by the negligence or the wrongful act or omission of employees of EPA, while acting within the scope of their employment, is in accordance with the provisions of the Federal Tort Claims Act, 28 U.S.C. ' ' 2671-80 and 40 C.F.R. Part 10.

10.2 No Warranty. Except as specifically stated in Article 7, neither party makes any express or implied warranty as to any matter whatsoever, including the conditions of the research or as to any Invention made or product developed, or the ownership, merchantability, or fitness for a particular purpose, of the research or any such Invention or product.

10.3 Indemnification. The Cooperator agrees to hold the Government harmless and to defend and indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by the Cooperator, its employees or any party acting on the Cooperator's behalf or with its authorization, of the Center's research and technical developments, the Center's facilities or equipment, or out of any use, sale or other disposition by the Cooperator, its employees or others acting on its behalf or with its authorization, of products made by the use of the Center's technical developments. This provision shall survive the termination of this Agreement.

10.4 Force Majeure. Neither party shall be liable for any event or circumstance beyond its reasonable control not caused by the fault or negligence of such party, which causes such party to be unable to perform its obligations under this Agreement (and which it has been unable to overcome by the exercise of due diligence), including but not limited to flood, drought, earthquake, storm, fire, pestilence, lightning and other natural catastrophes, epidemic, war, riot,

civil disturbance or disobedience, strikes, labor dispute, sabotage of the Center facilities, or any order or injunction made by a court or public agency. In the event of the occurrence of such a force majeure event, the party unable to perform shall promptly notify the other party. It shall further use its best efforts to resume performance as quickly as possible and shall suspend performance only for such period of time as is necessary as a result of the force majeure event.

10.5 Cooperator. The Cooperator agrees that during the term of this Agreement it will carry liability insurance in the amount set forth on the attached certificate of insurance to cover any liability to the Government or to Government employees and private individuals that may arise as a result of negligent acts or omissions of any of the Cooperator's employees or agents while they are performing work under this Agreement including any work which such employee or agent may be performing at the Center.

Article 11. Miscellaneous

11.1 No Benefits. No member of, or delegate to the United States Congress, or resident commissioner, shall be admitted to any share or part of this Agreement, nor to any benefit that may arise therefrom. This provision shall not be construed to extend to this Agreement if the Agreement is made with the Cooperator for the Cooperator's general benefit.

11.2 Governing Law. The construction, interpretation, validity, performance and effect of this Agreement for all purposes shall be governed by the laws applicable to the federal government.

11.3 Headings. Titles and headings of the Sections and Subsections of this Agreement are for the convenience of references only and do not form a part of this Agreement and shall in no way affect the interpretation thereof.

11.4 Waivers. None of the provisions of this Agreement shall be considered waived by any party hereto unless such waiver is given in writing to all other parties. The failure of any party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, shall not be deemed a waiver of any rights of any party hereto.

11.5 Severability. The illegality or invalidity of any provisions of this Agreement shall not impair, affect or invalidate the other provisions of this Agreement.

11.6 Amendments. If either party desires a modification to this Agreement, the parties shall, upon reasonable notice of the proposed modification by the party desiring the change, confer in good faith to determine the desirability of such modification. Such modification shall not be effective until a written amendment is signed by all the parties hereto by their representatives duly authorized to execute such amendments.

11.7 Assignment. Except as otherwise permitted herein, neither this Agreement nor any rights or obligations of any party hereunder shall be assigned or otherwise transferred by either

party without the prior written consent of the other party. However, the Cooperator may assign this Agreement to the successors or assignees of a substantial portion of the Cooperator's business interests to which this Agreement directly pertains.

11.8 Notices. All notices pertaining to or required by this Agreement shall be in writing and shall be signed by an authorized representative and shall be delivered by hand or sent by certified mail, return receipt requested, with postage prepaid, addressed as follows:

If to the Cooperator:
Karine COLETTE
Lawyer
25-29 quai Aulagnier
92600 Asnières
FRANCE

If to the Center:
Karen Dean
National Center for Computational Toxicology
Mail Drop B205-01
U.S. EPA
Research Triangle Park, NC 27711
USA

Any party may change such address by notice given to the other party in the manner set forth above.

11.9 Independent Parties. The relationship of the Center and the Cooperator is that of independent parties and not as agents of each other or as joint venturers or partners. The Center shall maintain sole and exclusive control over its personnel and operations. The Cooperator shall maintain sole and exclusive control over its personnel and operations.

11.10 Use of Name or Endorsements. The Cooperator shall not use the name of the Center or EPA, on any product or service which is directly or indirectly related to either this Agreement or any patent license or assignment agreement which implements this Agreement, without the prior approval of the Center. By entering into this Agreement the Center does not directly or indirectly endorse any product or service provided, or to be provided, by the Cooperator, its successors, assignees, or licensees. The Cooperator shall not in any way imply that this Agreement is an endorsement of any such product or service. This section in no way prohibits the publication of any EPA indication or statement regarding the efficacy of any Subject Invention and/or any other results of this Agreement.

11.11 No Approval. Nothing in this Agreement shall be deemed to constitute regulatory or scientific approval of the use of any particular product or technology. The Cooperator agrees that (a) nothing in this Agreement relieves it of any obligation to comply with applicable federal, state, or local laws, regulations, or requirements, and (b) possession or acquisition by the Center

Attachment A

Statement of Work ("SOW")
Cooperative Research and Development Agreement (ACRADA@)
between U.S Environmental Protection Agency ("EPA")
and L'OREAL Advanced Research

I. Goal

EPA's National Center for Computational Toxicology (NCCT) and L'OREAL are interested in the further research and development of the ToxCast™ predicative toxicology technology and its utilization by private and public entities. L'OREAL desires to provide resources for NCCT's development and evaluation of the ToxCast™ predicative toxicology technology using chemicals of scientific interest to L'OREAL.

II. Research Plan

EPA and L'OREAL will select a consensus set of 5 to 20 chemicals for Phase II of ToxCast™, and these 5 to 20 chemicals will be run by EPA through the over 400 assays available through the ToxCast™ contractors (www.epa.gov/ncct/toxcast). Chemicals will be run through the ToxCast™ assays in single-concentration screening format when appropriate, and then all positive compound-assay combinations will be followed up in multiple concentration-response format. Results for these 20 Phase II chemicals will be combined with the hundreds of other Phase II chemicals being run through the >400 assays, and analyzed relative to the results from the ToxCast™ Phase I training dataset derived for 320 chemicals. All results from both Phase I and Phase II of ToxCast™ will be made wholly available to L'OREAL, as well as the analysis of these result by the scientists of the NCCT.

III. Estimated Value and Benefits

A. Value of Contributions

1. Estimated value of EPA contributions (in-kind): $12,000,000.00
   ToxCast Phase™ I data- $6,000,000.00
   ToxCast Phase™ II data- $6,000,000.00

2. Value of L'OREAL's estimated contribution (in-kind): $1,000,000.00
   [Toxicity data on ToxCast Phase™ I and II chemicals]
   L'OREAL's cash contribution to EPA: ~~$400,000.00~~ $100,000.00
   L'OREAL's total contribution (cash and in-kind): $1,400,000.00 $1,200,000.00

B. Benefits of Cooperative Effort

1. For EPA: L'OREAL will fund 20 or more additional compounds to be run in the EPA ToxCast™ assays for Phase II, strengthening this dataset and enhancing the ability to predict toxicity for use by EPA Program Offices in environmental chemical prioritization. ToxCast™ is providing an innovative solution to a persistent and pervasive issue facing EPA regulatory programs: there are too many environmental chemicals for current testing guidelines to even start

characterizing hazard. ToxCast will address long-term goal II of ORD's Computational Toxicology Research Program Implementation Plan, providing EPA Program Offices advanced hazard characterization tools to prioritize and screen chemicals for toxicological evaluation. ToxCast™ is part of EPA's Office of Research and Development Computational Toxicology Research Program Implementation Plan (www.epa.gov/comptox/pdf/ORD_NCCT_Imp_Plan.pdf).

2. For L'OREAL: EPA's ToxCast™ program will generate toxicity predictions for chemicals of interest to L'OREAL's goals. Furthermore, will gain access to the complete ToxCast™ datasets and EPA experience in using these for predictive toxicology. ToxCast™ will help L"OREAL meet the challenging deadlines for moving to non-animal alternative toxicity testing for cosmetics under European REACH legislation.

AMENDMENT NO 1.
COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT
BETWEEN
L'OREAL
AND
THE NATIONAL CENTER FOR COMPUTATIONAL TOXICOLOGY
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

This "Amendment No. 1" is entered into by and between L'OREAL, a French Corporation which has its principal place of business at 14 rue Royale, 75008 PARIS, FRANCE ("the Cooperator"), and the National Center for Computational Toxicology ("the Center") of the U.S. Environmental Protection Agency ("EPA") under the authority of Title 15, United States Code ' 3710a, et seq. (commonly known as the Federal Technology Transfer Act of 1986).

WITNESSETH:

A. **WHEREAS**, the Cooperator and the Center executed a Cooperative Research and Development Agreement, effective October 20, 2008 (C080427) ("Agreement");

B. **WHEREAS**, the Cooperator and the Center want to amend and supplement the Agreement;

C. **WHEREAS**, the Cooperator and the Center want to add an additional research project to the agreement which is outlined in the Statement of Work provided in Attachment A.

D. **WHEREAS**, the Center views its continued cooperation with the Cooperator to be in furtherance of the public interest;

NOW, THEREFORE, the parties amend and supplement the Agreement as follows:

1. Paragraph 1.9, Technology is supplemented by adding as area: "Systemic toxicity".
2. Paragraph 2.1, Statement of Work is supplemented by adding: "The SOW shall be expanded to include the additional research project as described in the Supplemental Statement of Work (see Attachment A).
3. Paragraph 2.3, Assigned Personnel, is amended by changing the Principal Investigator for the Center to David Reif.
4. Paragraph 4.1, Transfer of Funds, is amended by adding the following: "The Cooperator agrees to pay an additional $1,000,000 to the Center for the performance of research specified in Article 2, as amended, and the Supplemental Statement of Work to be paid according to the schedule provided in Attachment B."

ATTATCHMENT A: Supplemental SOW

Added Statement of Work ("SOW")
Cooperative Research Development Agreement ("CRADA)
between U.S. Environmental Protection Agency ("EPA")
and L'OREAL Advanced Research

Project Proposal:
L'Oréal - U.S. EPA Development of ToxCast High Throughput Non-Animal Assessment Methods for Chronic and Sub-Chronic Non-Cancer Risk to Human Health

L'Oréal participants:
Jean-Roch Meunier (Head, Biological models and predictive method development department), Pascal Berthe (Head, Regulatory toxicology department), Sophie Loisel-Joubert , Gladys Ouédraogo (L'Oréal point of contact), Reine Note, Chafika Chettaoui, Hicham Noçairi.

U.S. Environmental Protection Agency, Office of Research and Development, National Center for Computational Toxicology (NCCT) participants:
Robert Kavlock (NCCT Director), David Dix (NCCT Deputy Director, EPA point of contact), Keith Houck, Richard Judson, Matt Martin, David Reif, Ann Richard.

I. Goal

EPA's National Center for Computational Toxicology and L'OREAL are interested in furthering the research and development of the ToxCast predictive toxicity technology and its utilization by private and public entities. L'OREAL desires to provide additional resources for NCCT to use to further develop and evaluate ToxCast by screening and evaluating chemicals that are of scientific interest to L'OREAL.

A three year collaborative project is proposed for the purpose of developing high throughput and non-animal testing and assessment methods for sub-chronic and chronic non-cancer risk to human health. This project is a continuation of the Statement of Work (SOW) being carried out under the existing Cooperative Research and Development Agreement (CRADA) between L'Oréal and EPA/ORD/NCCT executed 20 October 2008. If approved by both parties Project Managers, this Project Proposal will be appended to the original CRADA SOW.

II. Description of statement of work's steps

Step 1 to be performed during year 1
The first year of this project will focus on expanding the ToxRefDB database (Martin et al, 2009) with sub-chronic and chronic animal toxicity data from registration studies and the peer-reviewed scientific literature focused on the 960 chemicals of ToxCast phases 1 and 2 (Dix et al.,

2007; Judson et al., 2010). There are data from approximately 600 sub-chronic rat, mouse and dog studies, on about 400 chemicals, currently in ToxRefDB (http://www.epa.gov/NCCT/toxrefdb/). It is estimated that there are sub-chronic data on approximately 600 additional chemicals that can be entered into ToxRefDB over the first two years of this collaboration. Similarly, there are data from approximately 600 chronic rat, mouse and dog studies, on over 400 chemicals, currently in ToxRefDB and it is estimated that there are chronic data on approximately 400 additional chemicals that can be entered into ToxRefDB over the first two years of this collaboration. In order to accomplish this first step in the project, L'Oréal will provide funding for a Student Service Contractor (SSC) to work at EPA and curate sub-chronic study data into the ToxRefDB database. This SSC will work closely with EPA and L'Oréal staff, as well as the Postdoctoral Fellow also being recruited for this project. The SSC will be responsible for curating sub-chronic and chronic data into ToxRefDB, and for conducting Quality Control steps to ensure accuracy in the database. The goal of this effort will be to develop a computable set of high quality, publicly available sub-chronic and chronic data on 1000 or more chemicals, including most or all of ToxCast phase 1 and 2 chemicals, pharmaceuticals, and other compounds of interest.

Also during the first year of the project, a Postdoctoral Fellow funded by L'Oréal to work at EPA will initiate development of predictive toxicity signatures for sub-chronic and chronic, non-cancer endpoints. This Fellow will be the key person executing the project plan, directing the SSC, communicating results to the L'Oréal and EPA partners, and publishing the data and analyses through EPA websites and peer-reviewed publications. The Fellow will identify critical non-cancer endpoints and high-incidence target organ effects in ToxRefDB from sub-chronic and chronic studies on the 300 chemicals of ToxCast phase 1. Utilizing ToxCast phase 1 data on 300 chemicals, the Fellow will build predictive models of sub-chronic and chronic toxicity endpoints. From these predictive models, biological pathways whose perturbation can lead to sub-chronic and chronic toxicity will be identified and ToxCast data from phase 1 can then be used to suggest prioritization for further testing (Reif et al., 2010), thresholds of regulatory concern, and quantitative points of departure for adversity based on the in vitro ToxCast effects of chemicals and chemical classes in these pathways (Judson et al., submitted; Rotroff et al., 2010). The details of these sub-chronic and chronic models will be published on EPA websites, and in a peer-reviewed journal article within the first two years of the Fellow's hiring.

Also during the first year of the Fellow's hiring, an analysis of current ToxCast phase 1 and 2 chemicals will be conducted in order to identify the highest value chemicals for additional ToxCast testing. This analysis will take into account sub-chronic and chronic animal toxicity data and other information, from ToxRefDB and other sources, indicating candidate chemicals that have particular toxicity profiles. The analysis will also look for information on what biological pathways, suggestive of mode of action, may be perturbed by these candidate chemicals. A list of at least 24 candidate chemicals will be developed by the Fellow based on combinations of animal toxicity, and potential modes of action, that nominate these chemicals as the highest value addition to ToxCast testing in the first year of this project. Both L'Oréal and EPA will review these nominations and decide on the mutual value of these chemicals going into ToxCast phase 2 testing. L'Oreal and EPA will jointly choose the compounds to be tested. L'Oréal will provide funding for the cost of testing at least these additional 24 chemicals selected

specifically to test the sub-chronic and chronic, non-cancer target organ predictive models developed in this project.

Step 2-1 to be performed during year 2

The second year of this project will see the completion of data curation into ToxRefDB for approximately 1000 ToxCast and other chemicals. These data will be made publicly available through EPA websites, and a peer-reviewed journal article. Using these ToxRefDB data on the ToxCast chemicals, the Postdoctoral Fellow will then be able to test and confirm the predictive sub-chronic and chronic models and pathway based thresholds using data on the 700 chemicals of ToxCast phase 2.

Step 2-2 to be performed between year 2 and year 3

The confirmation of model performance obtained in Step 2 will be enhanced by the additional 24 chemicals in phase 2 of ToxCast made possible by this L'Oréal-EPA collaboration. Pathways leading to non-cancer effects in the liver, kidney, thyroid, spleen, adrenal, lung, testis and other target organs (http://www.epa.gov/NCCT/toxrefdb/) are likely to involve a diverse range of pathways and organotypic cellular processes. While some pathways and cell systems are already well represented in ToxCast (e.g endocrine, nuclear receptor signaling, hepatic), others will benefit from the ongoing addition of more ToxCast assays from newly awarded EPA contracts (e.g., Odyssey Thera) that will also be providing data on the 1000 phase 1 and 2 chemicals during the first year of this L'Oréal-EPA project. Thus at the end of two years, this project will have produced a rich in vivo and in vitro database on 1000 or more chemicals, and robust models for predicting sub-chronic and chronic toxicity. With extrapolation of dose-response from in vitro to in vivo (Rotroff et al., 2010), and appropriate modeling of other uncertainties (Judson et al., in press), it will be possible to incorporate the model and pathways data based on in vitro results for the assessment of sub-chronic and chronic risk to humans. All of the results from these studies and analyses will be published on EPA websites and in peer-reviewed journal articles in a timely fashion.

Step 3 to be performed during year 3

In the third year of this project, the Postdoctoral Fellow and L'Oréal-EPA collaborators will focus on critical case study applications of the methods, models and decision support tools developed during the first two years. Case studies will be carefully selected to support the goals of the collaboration in developing the ability to predict sub-chronic and chronic, non-cancer hazard from chemical exposures and support high throughput risk assessments based on alternatives to animal testing.

Miscellaneous

Knowledge and tools derived from this collaboration will be made available to L'Oréal in a timely fashion, essentially as soon as they are developed and become available.

The Postdoctoral Fellow will visit L'Oréal once per year to transfer and discuss these tools and data directly with L'Oréal staff (travel expenses provided by L'Oréal are described below in Section V of this SOW).

In addition, L'Oréal will reimburse any reasonable and duly evidenced travel, accommodation and out-of-pocket expenses necessarily incurred by the Postdoctoral Fellow, at L'Oréal's express

request, for at least two additional visits to L'Oréal in Paris.

Several types of deliverables can be expected from this collaboration:

- Predictive models of various types of sub-chronic and chronic toxicities, similar to the liver cancer model in Judson et al., 2010, and the reproductive toxicity model in Martin et al., 2011 in press.
- Weight of evidence models similar to those developed for endocrine disruption (Reif et al 2010), and hepatic cancer (Shah et al 2010).
- Databases supporting model development and validation of model performance.

These databases, interfaces and query tools, and models will all be developed using open-source software such as MySQL, Java, PERL, and the statistical programming language R. Use of these open-source tools will facilitate exchanges between EPA and L'Oréal, as well as subsequent publication and sharing of these resources at large.
All open source software packages used for the developments described above, should originate from the CRAN package repository for the R-language packages and from the CPAN package repository for the PERL packages.

III. Governance

Close collaboration between EPA and L'Oréal will be maintained through regular interactions by scientific staff and management, including the Postdoctoral Fellow and Student Service Contractor. Tele- or Video-conferences will be held at least monthly. During these conferences, a L'Oréal representative will participate in person when possible at the EPA. Face-to-Face meetings with all stakeholders will be held at least twice per year. As provided for in Section II of this SOW, in addition to these meetings, it is expected that the Postdoctoral Fellow will visit L'Oreal's teams in Paris, France 3 times per year. Following these meetings, minutes will be drafted and shared with all participants.

IV. Benefits of cooperative effort:

1. For EPA: Additional data on 1,000 chemicals from both animal toxicity studies and ToxCast screening will be added to EPA's Chemical Toxicity databases. In addition, the data will be used to develop predictive tools (models and signatures) that EPA can use to help predict potential toxicity and prioritize limited chemical screening resources. ToxCast™ is providing an innovative solution to a persistent and pervasive issue facing EPA regulatory programs: there are too many environmental chemicals for current testing guidelines to even start characterizing hazard. ToxCast addresses the goal of EPA ORD's Computational Toxicology Research Program Implementation Plan which is to provide high-throughput decision support tools for screening and assessing chemical exposure, hazard and risk. (Full implementation plan: http://epa.gov/ncct/download_files/basic_information/CTRP2_Implementation_Plan_FY09_12.pdf)

2. For L'OREAL: Access to chemical toxicity data, ToxCast profiles, predictive models and signatures that they can use to assess chemicals that interest them.

V. Estimated Value:

- Value of EPA contributions (in-kind):
  - ToxCast Phase 1 and 2 data (1000 chemicals)- $25,000,000.00
  - ToxRefDB data (current sub-chronic and chronic 600 studies)- $30,000,000.00

- Value of L'Oréal contributions:

Cash:

- Student Services Contractor at EPA for two years- $116, 000.00
- Postdoctoral Fellow at EPA for 3 years- $270,000.00
- Travel expenses for Postdoctoral fellow: $14,000
- At least 24 additional ToxCast chemicals- $600,000.00
- Total- $1,000,000.00 from L'Oréal to EPA.

In-Kind:

- Toxicity and metabolic data on select ToxCast chemicals- $1,000,000.00
- L'Oréal will provide throughout the project an intellectual input in the following areas: metabolism, physical-chemical properties, statistics and mathematical modeling.

A formal reporting of the budget will be provided by the US EPA each year. Any money saved for the performance of Step 1, Step2-1 and Step 3, may be allocated to the testing of extra chemicals, at L'Oréal's request.

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ATTATCHMENT B: Funding Schedule

Funding for Step 1 Year 1:
$ 58.000 for Student Services
+ $ 90.000 for Postdoctoral Fellow
+ $ 4.660 for one trip to France (lump sum fee)
= $ 152.660,00

Funding for Step 2-1 Year 2:
$ 58.000 for Student Services
+ $ 90.000 for Postdoctoral Fellow
+ $ 4.660 for one trip to France (lump sum fee)
= $ 152.660,00

Funding for Step 2-2 upon establishment of the list of chemicals:
The estimated duration of the testing is 6 months.
At least 24 chemical compounds shall be tested for a lump sum of $600.000.

Funding for Step 3 Year 3:
$ 90.000 for Postdoctoral Fellow
+ $ 4.680 for one trip to France (lump sum fee)
= $ 94.680,00

L'OREAL shall pay the aforementioned total amount for each Step before work begins, upon receipt of a request for funding sent by the US-EPA by mail.