

MATERIALS COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

This Materials Cooperative Research and Development Agreement (“Materials CRADA” or “Agreement”) is entered into by and between European Commission Joint Research Centre (JRC) Directorate F – Health and Food Unit F.3 – Systems Toxicology, incorporating the EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) which has its principal place of business at Via E. Fermi 2749, Ispra, Italy (the Collaborator), and the United States Environmental Protection Agency (“EPA”) Center for Computational Toxicology and Exposure (CCTE), under the authority of Title 15, United States Code §§ 3710a-3710d (commonly known as the Federal Technology Transfer Act of 1986).

1. Research Material. CCTE agrees to transfer to the Collaborator the following (the “Research Material”):
 - (1) 2-3 Frozen vials of HepG2-AR2 cells
 - (2) 220 Frozen stocks of DMSO-solubilized test chemicals
 - (3) Standard operating procedure for AR2 assay (agonist mode)
 - (4) Standard operating procedure for AR2 assay (antagonist mode)

This Materials CRADA involves no other exchange of personnel or resources.

2. Human Subjects Research Ethics and Oversight. The Research Material does not involve specimens or data derived or collected from human subjects and therefore does not need review and approval by the Human Subjects Research Review Official (HSSRO).
3. Dual Use Research of Concern (DURC). The DURC Internal Review Entity (IRE) has determined that this research does not meet the DURC definition and that no additional review and oversight under the *USG Policy for Institutional Oversight of DURC* are required. The Principal Investigator (PI) must report to the IRE any results or changes in the research such that one or more of the 7 experimental effects of concern may apply, or if the PI feels that the research may be DURC.
4. No Transfer. Collaborator’s investigator agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under his/her direct supervision without advance written approval of CCTE. When the Research Project is completed, the Research Material will be returned to the CCTE or disposed, if directed by CCTE, to the extent such destruction is permitted by law. CCTE reserves the right to distribute the Research Material to others and to use it for its own purposes.
5. Proprietary Information. The Collaborator shall place a proprietary notice on all information

that it delivers to CCTE under this Agreement which it asserts is Proprietary Information of the Collaborator. CCTE agrees that: (1) any information designated as Proprietary Information which is furnished by the Collaborator to CCTE under this Agreement; (2) any information obtained by either party during the performance of this Materials CRADA that would be claimed as Proprietary Information had it been submitted by the Collaborator; or (3) any information furnished by the Collaborator in contemplation of this Agreement shall be treated as Proprietary Information and will be used by CCTE 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 Collaborator, 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. CCTE agrees to use its best efforts to protect the information designated as Proprietary Information from unauthorized disclosure. The Collaborator agrees that CCTE is not liable for the disclosure of Proprietary Information which, after notice to and consultation with the Collaborator, 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 Collaborator.

6. No Warranty. The Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO THE RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. CCTE is entitled to transfer this Research Material or sublicense the rights to use the Research Material to the Collaborator in accordance with the provisions of this Agreement. CCTE makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties. CCTE shall not be liable for any claims or damages arising from the Collaborator's use of the Research Material; however, no indemnification is provided or intended.
7. Intellectual Property. CCTE and the Collaborator 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, CCTE and the Collaborator will negotiate a standard CRADA in good faith. The standard CRADA 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. For the purposes of this section, "Subject Invention" means any invention, conceived or first actually reduced to practice in the performance of this Agreement, and "Computer Software" means computer software, computer programs, computer data bases, and documentation thereof developed in whole or in part under this Agreement.

8. Disputes. 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 forty-five (45) days after submission of the dispute for resolution, the matter shall be submitted by EPA to the Administrator of EPA or the Administrator's designee for resolution. However, nothing in this Agreement will prevent the Collaborator from pursuing other remedies that may be available under applicable laws in a court of competent jurisdiction.
9. Privileges and Immunities. Nothing in this Agreement shall constitute or be considered to be a limitation upon or a waiver of any of the privileges and immunities of either Party.
10. Severability. The illegality or invalidity of any provisions of this Materials CRADA shall not impair, affect, or invalidate the other provisions of this Materials CRADA.
11. Assignment. Neither this Materials CRADA 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.
12. 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 (including private courier mail service) or sent by certified mail, return receipt requested, with postage prepaid, addressed as follows:

(a) If to the Collaborator:

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(b) If to CCTE:

Russell Thomas
U.S. EPA Center for Computational Toxicology and Exposure (CCTE)
109 T.W. Alexander (MD-D-143-02)
Research Triangle Park, NC 27711
919.541.5776
thomas.russell@epa.gov

With a copy to:

Samantha Plishka
Extramural Management Analyst
U.S. EPA Center for Computational Toxicology and Exposure (CCTE)
109 T.W. Alexander (MD-B-205-01)
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AND

Kathleen Graham
Manager
Federal Technology Transfer Act Program
1595 Wynkoop St.
Denver, CO 80202-1129
Telephone: (303) 312-6137
Email: graham.kathleen@epa.gov

Either party may change the contact information set out above by notice given to the other party in the manner set forth above.

13. No Endorsement. By entering into this Materials CRADA, CCTE does not directly or indirectly endorse any product or service provided, or to be provided, whether directly or indirectly related to either this Materials CRADA or to any patent or other intellectual property license or agreement which is related to this Materials CRADA. The Collaborator shall not in any way state or imply that this Materials CRADA is an endorsement by the U.S. Government or any of its organizational units or employees of any such product or service.
14. Termination. Either the CCTE or the Collaborator may unilaterally terminate this entire Agreement at any time by giving written notice to the other party at least thirty (30) calendar days prior to the desired termination date.
15. Entire Agreement. This Materials CRADA constitutes the entire agreement between the parties and supersedes any prior understanding or written or oral agreement.
16. Interpretation. U.S. federal contract law principles will be used for interpretation of this Agreement in the context of a difference of opinion between the Parties.
17. Power and Authority. The undersigned expressly certify and affirm that the contents of any respective statements made or reflected in this Materials CRADA are truthful and accurate and that the signatories hereto have the authority to bind their respective organizations to this

Agreement.

- 18. Effective Date. This Materials CRADA shall be effective upon execution by the parties when the last signatory has signed the Agreement.
- 19. Duration. The term of this Materials CRADA is sixty (60) months from execution.
- 20. The provisions of Articles 3, 4, 5, 6, 7, 8, 9, and 15 shall survive the termination of this Materials CRADA.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives as follows:

For CCTE:

By:  _____ Date _____


For the Collaborator:

By:  _____ Date _____


APPENDIX A

RESEARCH PLAN

The EPA Office of Research and Development (ORD) has developed a new assay to measure androgenic effects of environmental chemicals. This new assay performed well internally but external validation by a reputable laboratory will be required for this new assay to be accepted as a possible alternative to animal testing under the Endocrine Disruptor Screening Program (EDSP). The Center will send HepG2-AR2 cells and frozen stocks of blinded test chemicals to the JRC. JRC will establish HepG2-AR2 cultures and optimize a workflow for testing chemicals for two protocols (agonist mode and antagonist mode) using control chemicals to confirm proper assay performance. JRC will then test the reference chemicals provided by the Center in triplicate experiments (minimally) and in multi-concentration response such that an activity threshold can be established for each assay mode and an activity call, maximal activity, half-maximal response concentration for each test chemical. The results from the validation testing may ultimately result in a published manuscript in which ORD staff would be co-authors.