OPPT-2008-0319

"Kristie Stoick"
<ksullivan@pcrm.org>
06/04/2008 07:08 PM

To NCIC OPPT@EPA, <auer.charles@epaemail.epa.gov>

cc "Chad Sandusky" <csandusky@pcrm.org>, "Martin Stephens" <mstephens@hsus.org>, "Jessica Sandler" <JessicaS@peta.org>, "Sara Amundson"

bcc

Subject Comments on ChAMP; Docket EPA-HQ-OPPT-2008-0319

Dear Mr. Auer,

Please find a letter and addendum attached in response to the call for public comments on the Chemical Assessment and Management Program (ChAMP), under docket EPA-HQ-OPPT-2008-0319.

Please respond with questions or concerns.

Sincerely,
Kristie Sullivan

****
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ChAMP letter--PCRM to EPA.pdf ChAMP Animal Welfare Guidance.pdf

CONTAINS NO CBI

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OPPT-2008-0319

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June 4, 2008

Mr. Charles Auer
Director, Office of Pollution Prevention and Toxics
Environmental Protection Agency - East
Room 3166
1201 Constitution Ave., NW
Washington, D.C. 20460

Docket Number: EPA-HQ-OPPT-2008-0319

RE: Comments on ChAMP: submitted electronically to auer.charles@epaemail.epa.gov and oppt.ncic@epa.gov.

Dear Mr. Auer,

I am writing on behalf of several animal protection organizations, including the Physicians Committee for Responsible Medicine, the Humane Society of the United States, Doris Day Animal League, and People for the Ethical Treatment of Animals, whose combined memberships include more than 12 million Americans.

As you know, our organizations were active stakeholders in the original HPV program, and have reviewed and commented on the vast majority of HPV test plans. Our comments were directed primarily at ways to reduce the animal testing proposed in this program. During the HPV program, EPA developed animal welfare guidance with input from our scientists and posted this guidance on the HPV website. This guidance may still be found at the following links (http://www.epa.gov/hpv/pubs/general/ceoltr2.htm and http://www.epa.gov/hpv/pubs/general/anfacs2.pdf), although it is clearly stated that this guidance has not been updated nor do there appear to be plans to do so for the newly announced Chemical Assessment and Management Program (ChAMP).

It is for this reason that I am providing to you in an attachment to this letter a brief summary of the original guidance under HPV as well as expanded guidance that we developed based on extensive review of test plans in HPV. The process of reviewing HPV test plans provided valuable experience in identifying the many ways in which proposed testing would have been either superfluous (e.g., insoluble materials and fish testing) or the resultant data difficult to interpret in terms of human and environmental health. These principles have been through a vetting process during the course of the original program, and are considered scientifically acceptable by many major stakeholders.

We therefore ask EPA to update the animal welfare guidance for participants in ChAMP and request that EPA notify the manufacturers of this updated guidance, both in a letter to participants and by posting the guidance on the ChAMP website. I would be more than willing to work with your scientific staff to further develop these principles.

The impetus to reduce and replace the use of animals in regulatory testing is growing stronger every year. As shown by the original HPV Program, throughout the course of just a few years new ideas are put into practice that could reduce the number of animals killed. There are a number of initiatives underway in the US and the European Union designed to explore ways to minimize traditional *in vivo* testing, by developing alternative *in vitro* or *in silico* test methods and by integrating weight-of-evidence and alternative approaches into testing strategies. As ChAMP begins, it would be prudent to include provisions that allow for continuous and consistent update of testing guidelines, in order to recommend the most updated assays, test guidelines, protocols, and/or approaches. Information along this line of thought is also included in the attached suggested animal welfare guidance.

Thank you for your attention. I look forward to your favorable response, and to working with EPA to further develop the animal welfare principles that are essential to the success of ChAMP.

Regards,

Chad B, Sandusky, PhD
Director of Research and Toxicology

Cc: Martin Stephens, Humane Society of the United States
Sara Amundson, Doris Day Animal League
Jessica Sandler, People for the Ethical Treatment of Animals
Kristie Stoick, Physicians Committee for Responsible Medicine

Animal Welfare in the Chemical Assessment and Management Program and the Extended High Production Volume Program

Animal welfare principles for EPA's original HPV Program participants are described in the *Letter to Manufacturers/Importers*,[1] which states that animal experiments should not be performed if another validated method is available. Additional principles allowed the maximum use of existing data in a weight-of-evidence approach that avoided check-the-box toxicology. For example, the formation of scientifically appropriate categories of related chemicals and use of structure activity relationships was encouraged. No terrestrial testing and no new dermal testing were to be conducted on HPV chemicals and no sub-chronic or reproduction studies were to be conducted with closed-system intermediates. Special consideration was given to GRAS (Generally Recognized as Safe) chemicals, and *in vitro* genotoxicity testing was recommended unless known chemical properties preclude this approach.

The Extended HPV (EHPV) Program and the Chemical Assessment and Management Program (ChAMP) should follow these guidelines, and, in addition, the animal welfare principles described briefly below, which are based on practical experience gained during the original HPV Program. These principles should also be followed in circumstances where the EPA may use outside contract support during the review process of company plans submitted under ChAMP and/or if the EPA decides to pursue rulemaking for specific chemicals.

Use of Combined Endpoint Screening Protocols If data are lacking on several endpoints for a candidate chemical, the use of protocols which combine these assessments into one study are appropriate for ChAMP and EHPV. This would be *in lieu* of conducting a separate study for each endpoint and greatly reduces animal use. For example, instead of conducting three studies according to OECD TG 408, 415/416, and 414 for the repeat dose, reproductive, and developmental endpoints, one study according to the OECD TG 422 protocol should be conducted. This would also be appropriate for individual areas of concern, e.g., an OECD screening protocol for potential reproductive/developmental effects (OECD 421) is sufficient for ChAMP and EHPV rather than a traditional 1- or 2-generation reproduction (OECD 415/416) and/or developmental study (OECD 414), again greatly reducing the number of animals used in testing.

Rapid Hydrolysis of Parent Chemical The candidate chemical need not be tested via oral exposure in animals if it hydrolyzes to well-characterized products in an aqueous environment at low pH. If available, existing data on the hydrolysis products may then be used to meet SIDS endpoints without additional testing. In some cases, this principle can be applied to known metabolites of the parent chemical, if the toxicological properties of these metabolites are well-known.

Acidic/Corrosive/Irritating Materials If a candidate chemical is known to be a strong acid, it may be completely ionized in aqueous environments and is expected to cause localized, corrosive effects in the GI tract and in the respiratory system. Unless a substance is neutralized, results from animal tests may be confounded by the corrosivity of the chemical and mammalian testing would not yield meaningful results. This can also be true for severely irritating chemicals. However, the results from a neutralized test substance may not be relevant to understanding the potential systemic effects from the non-neutralized test substance i.e., the product in commerce. The effect of these confounding factors on the interpretation of results (e.g., the extrapolation to human health effects) of testing such materials in animals should be carefully evaluated prior to conducing *in vivo* tests.

Highly Reactive Materials Mammalian and/or ecotoxicity testing with candidate chemicals that are highly reactive to air and/or water, as demonstrated by physical/chemical data, may not be feasible.

Gases Candidate chemicals in gas form may present several concerns, including flammability and/or explosive potential at test levels and the potential for asphyxiation of test subjects versus systemic toxicity

[1] Wayland SH. (1999) Letter to manufacturers/importers. See http://www.epa.gov/chemrtk/ceoltr2.htm.

per se. Additionally, some gases are minimally toxic and rapidly excreted. Thus, chemical and physical properties may impact the ability to perform testing and additional testing may not yield meaningful results.

Complex Mixtures Additional testing with a variable mixture may not provide additional useful information and existing data on major constituents of the candidate mixture may be sufficient to fill SIDS endpoints.

Weight-of-Evidence Several considerations that may apply to a candidate chemical could, if utilized, lead to a reduction or elimination of *in vivo* testing and should be considered before plans for testing are undertaken. For example, where histopathology data on reproductive organs from a subchronic study are available and show no effects, these data in combination with an available developmental study may eliminate additional testing for reproductive toxicity.[2] In some cases, traditional reproduction/developmental studies may be avoided if existing data from other studies, i.e. 2-year cancer bioassays, have evaluated reproductive and developmental parameters. Moreover, a separate developmental study may be avoided if data are available from one- or two-generation reproduction studies. Dermal systemic testing may be avoided if studies (*in vitro*, *in silico*, or existing *in vivo*) show little potential for percutaneous absorption of the candidate chemical.[3] Finally, if higher-tier toxicity tests have been conducted, lower-tier screening tests may not be needed for the purposes of ChAMP or EHPV.

Methods to Reduce Fish Toxicity Testing Recently, a new fish acute threshold (step-down) test strategy has been described for new chemicals[4] and human pharmaceuticals,[5] based on the observation that fish are rarely more sensitive than algae and daphnia. It is proposed that the fish median lethal concentration (LC50) test may be replaced with an acute threshold test in which fish testing would be performed at one concentration only (the lowest EC50 concentration obtained with previous algae and daphnia testing). This approach is predicted to reduce the total number of fish used by approximately 73%.

Additional Tools and Concepts to Consider as ChAMP is Implemented
While there is currently no international consensus for applying weight-of-evidence (WoE) approaches, work at several agencies, including the OECD, the USEPA, ILSI, and RIVM is ongoing and should be given consideration for inclusion into ChAMP as appropriate. The Dutch chemicals agency RIVM has recently completed a report investigating the potential for the use of Integrated (or Intelligent) Testing Strategies (ITS) under the new European REACH legislation.[6] Considerations that may apply to ChAMP include an investigation of the regulatory impact of a 2-generation reproduction test (versus a 1-generation). The report also gives a more general discussion of alternative methods and ITS, including (Q)SARS and chemical categories, *in vitro* studies, toxicogenomics, and exposure-based waiving of testing; a WoE approach using Bayesian analysis of existing information from all potential sources makes this report a useful tool for anyone designing a plan for the testing of a candidate chemical.

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[2] OECD Secretariat (2004) Manual for Investigation of HPVChemicals. (Section 4.3) See http://www.oecd.org/dataoecd/35/38/31179717.pdf.
[3] Stoick *et al.* (2007) Systemic testing by the dermal route can be precluded by new non-animal percutaneous absorption strategies. Proc. 6th World Congress on Alternatives and Animal Use in the Life Sciences. AATEX **14**, Special Issue: 561-564.
[4] Jeram S *et al.* (2005) A strategy to reduce the number of fish in acute ecotoxicity testing of new chemical substances notified in the European Union. *Reg Tox Pharm* 42: 218-224.
[5] Hutchinson TH *et al.* (2003) A strategy to reduce the numbers of fish used in acute ecotoxicity testing of pharmaceuticals. *Environ Toxicol Chem* 22: 3031-3036.
[6] Vermeire TG *et al.* (2 May 2007) Selected Integrated Testing Strategies (ITS) for the risk assessment of chemicals. Rijksinstituut voor Volksgezondheid en Milieu RIVM. Available at: http://hdl.handle.net/10029/13400.

Work is also ongoing to determine ways to avoid additional *in vivo* genotoxicity testing while satisfying concerns regarding high rates of false positive results for *in vitro* tests. Attention should be given to any work in this area before commencement of *in vivo* genotoxicity testing.[7,8]

Broad international support for WoE approaches was shown at a December 2007 OECD workshop titled Integrated Approaches to Testing and Assessment. Principles that will be followed during the REACH process in an attempt to maximally avoid *in vivo* testing were presented, and include:

- Existing human and animal information
- Non-test based info (QSAR, categories)
- Weight of evidence
- Non-guideline toxicity tests
- *In vitro* methods
- Situations where testing is not feasible
- No requirements for polymers and intermediates with no exposure
- Exposure-driven regulations
- Evaluation of testing proposals

More information can be found on the European Chemicals Bureau Web site: http//ecb.jrc.it. While some of these considerations are already taken into account as part of established animal welfare principles, others are not and deserve careful consideration.

In addition, the workshop summary and recommendations for future work, once published, have the potential to be valuable tools for those seeking to use QSARS, WoE, and other "alternative" approaches to fulfilling chemical hazard information needs.

At the USEPA, work is also ongoing to develop specific *in vitro* assessment methods and strategies, such as the efforts of the National Center for Computational Toxicology's ToxCast Program. As ChAMP is implemented, it will become clearer how participants can take advantage of them.

Finally, since the advent of the original USEPA HPV Program, a number of online tools for determining chemical hazards have been created. The first, eChemPortal, draws together available data from many sources to provide master search capabilities. This free service is available at http://webnet3.oecd.org/echemportal/. The second is the OECD QSAR Toolbox, the first version of which was just made available in March of 2008. Download instructions can be found at www.oecd.org/env/exisingchemicals/qsar. The Toolbox is a library of hazard information and QSAR models, and can extrapolate missing experimental values by read-across and trend analysis. These *in silico* tools are only going to become more relevant as interest increases, and ChAMP participants should be required to consider using these and other tools as part of any participation plan.

These tool and concepts should always be employed before consideration of new *in vivo* testing, in conjunction with the animal welfare considerations outlined above.

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[7] Kirkland DJ *et al.* (2007) *In vitro* approaches to develop weight of evidence and mode of action discussions with positive *in vitro* genotoxicity results. *Mutagenesis* 22(3):161-175.

[8] Kirkland DJ *et al.* (2007) How to reduce false positive results when undertaking *in vitro* genotoxicity testing and thus avoid unnecessary follow-up animal tests: Report of an ECVAM Workshop. *Mutation Research* 628:31-55.