April 18, 2006

Dr. Michael D. Shelby, CERHR Director
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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Submitted electronically to shelby@niehs.nih.gov

Dear Dr. Shelby,

The following comments are submitted on behalf of the more than one million members and supporters of People for the Ethical Treatment of Animals (PETA), in response to the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea which was prepared in January, 2007. PETA is the world's largest animal rights organization and is committed to using the best available science to protect animals from suffering and to promoting the acceptance of alternatives to animal testing.

General comments regarding the chemical evaluation process

According to the NTP-CERHR web site,[1] public comment is solicited at three steps in the chemical evaluation process. Despite this, there is no opportunity for meaningful public comment on the most significant findings produced by this process, namely, the identification of critical data needs by the expert panel and on the new studies recommended as a result. Although comment is accepted on what is called the Draft Expert Panel Report, this is misleading, since this document is only a partial draft that does not include the critical data needs section. In fact, critical data needs are first identified in the final document, the Expert Panel Report. While comment is again accepted at this time, the report is finished at that point and has already been published. It is, therefore, too late for public comment to affect the report's content. At best, any comment received will be bundled together with the finished report in a monograph that is assembled retrospectively. In practice, even this outcome seems uncertain, since only two of PETA's many comments have ever been included in a monograph.[2,3]

Accepting comment on the incomplete draft report does not sufficiently provide for meaningful input from the public on the final document, since interested parties, such as PETA, can only guess at which new studies might be called for at this step. Further, in those cases in which PETA has commented on a draft report, such as that for acrylamide, our comment was not mentioned in the final document, and was apparently not considered in its preparation.[4] If the NTP-CERHR were truly interested in public comment it would allow interested parties the opportunity to comment on critical data needs identified by the expert panel report, and on the studies recommended as a result, at a point in the process in which such comment could actually affect the content of the final report. Instead, what the agency does is provide several 'opportunities' for public comment at steps in the process at which such comment can have only minimal effect.

Specific comments regarding the Expert Panel Report

Hydroxyurea has been used as an anti-cancer drug for more than 40 years and, in 1998, it was approved by the FDA for the treatment of sickle cell disease.[5] It is marketed by Bristol-Myers Squibb under the names Hydrea® and Droxia®. As stated in the report, the use of hydroxyurea in children has been reported frequently. Hydroxyurea is not recommended for use during pregnancy, but pregnant women may be exposed if they conceive while on therapy.

Considering hydroxyurea's long and extensive history of clinical use, it is not surprising that it has been extremely well studied. The expert panel itself evaluated more than 125 separate studies in preparing its report. Nearly one-third of these are on human patients, including 36 on children. Commendably, the expert panel recommends addressing most of the critical data needs identified by analysis of existing patient data and new studies on relevant patient populations. These are to include: 1) systematic follow-up of pregnancy outcomes to assess hydroxyurea's potential developmental toxicity to the fetus and newborn following maternal exposure during pregnancy and lactation, 2) long-term studies assessing growth and development in exposed children with sickle cell disease younger than five years of age, and 3) studies assessing fertility and potential reproductive effects in people exposed as infants, children, adolescents, and adults. An ideal opportunity clearly exists for Bristol-Myers Squibb and other interested parties to determine the real effects of hydroxyurea on large populations of human patients through Phase IV, post-marketing studies.

Inexplicably, however, multi-generation animal studies are also recommended to address the same data needs mentioned above, in particular, the long term effects of prenatal and postnatal hydroxyurea exposure on postnatal development. Each of these studies can be expected to cause the deaths of thousands of animals. Such duplicative testing on animals for hydroxyurea is unnecessary and completely unjustified, especially when human data are so readily obtainable and will necessarily be more applicable to addressing any data needs. Further, since hydroxyurea's use has been approved by the FDA, it has already been the subject of all required animal and clinical studies. The more than 75 animal studies evaluated in preparing this report span more than ten species ranging from insects to primates. They have already produced NOAELs for reproductive and developmental endpoints in rats and mice including embryo implantation and developmental neurotoxicity.[6,7,8,9,10,11,12] Rather than supporting the relevance of any proposed new animal studies to predicting hydroxyurea's effects in humans, the existing data instead suggest that species vary in their sensitivity to hydroxyurea with mice being more sensitive than rats who are, in turn, twice as sensitive as primates.[13,14] It is therefore inconceivable that more studies consuming thousands of animals will provide data relevant to humans that cannot be more readily obtained by analysis of the real effects of hydroxyurea on an even greater number of human patients.

Additional studies are also recommended to address hydroxyurea's effects at a mechanistic level. Although not stated in the report, it is our hope that preference will be given to *in vitro* studies to address this data need. More than 25 studies addressing the

mechanism of hydroxyurea's effects, eight of which were conducted *in vitro,* were evaluated in preparing this report. In one case,[15] the expert panel specifically notes the validation of *in vivo-in vitro* comparisons. Existing data suggest that hydroxyurea produces toxicity through inhibition of DNA synthesis with consequent arrest of the cell cycle and cell death – processes that are especially well-suited to further study *in vitro.*

Finally, we must repeat our request of July 8, 2004 that the NTP-CERHR give more consideration to possible duplication between its programs and those of other governmental bodies. As was the case with fluoxetine, it is unclear why the NTP-CERHR is considering hydroxyurea, a drug that would appear to be the responsibility of the FDA. The expert panel itself notes that hydroxyurea is currently being investigated for use in children as young as 6 months old with sickle cell disease by the National Heart, Lung, and Blood Institute. This follows a phase II study of hydroxyurea in children which demonstrated that the drug does not adversely affect growth and development between the ages of 5 and 15 and a pilot study of hydroxyurea in children between the ages of 6 months and 24 months which demonstrated that the drug is tolerated well by small infants.[16] There have been other instances in which the NTP-CERHR's work appears to overlap with that of other agencies. For example, in 2001 and 2002, both the NTP and the EPA requested additional animal data on methanol. Even the director of NIEHS at the time, Dr. Ken Olden, expressed surprise at this overlap in a 2002 Toxicology Forum in Aspen, Colorado, and stated that the NTP could have saved taxpayer funds had it known that the EPA was conducting similar studies. As it currently stands, it appears that the NTP-CERHR is responsible for the continued use of large numbers of animals in clearly redundant testing.

In conclusion, we strongly object to the expert panel's recommendation that thousands of additional animals be used in studies of the reproductive and developmental toxicity of hydroxyurea, an already well-studied drug with a 40-year history of clinical use that is currently regulated by the FDA. In addition, we once again urge the NTP-CERHR to reevaluate its chemical evaluation process in order to provide an opportunity for public comment on the critical data needs identified by the expert panel at a step in the process at which such comment is still meaningful, and we request that the NTP-CERHR give more consideration to possible duplication between its programs and those of other governmental bodies.

Please feel free to contact me at 610-586-3975 or via e-mail at JosephM@peta.org if you have any questions.

Sincerely,

Joseph Manuppello
Research Associate, Regulatory Testing Department
People for the Ethical Treatment of Animals

[1] NTP-CERHR. About CERHR. 2007. Available at http://cerhr.niehs.nih.gov/aboutCERHR/index.html#evalprocess

[2] NTP-CERHR. 2006. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di(2-Ethylhexyl) Phthalate (DEHP). U.S. Department of Health and Human Services. NIH Publication No. 06 - 4476

[3] NTP-CERHR. 2003. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methanol. U.S. Department of Health and Human Services. NIH Publication No. 03-4478.

[4] NTP-CERHR. 2004. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Acrylamide.

[5] Williams, V. L. 2004. Pathways of Innovation - a history of the first effective treatment for sickle cell anemia. *Perspectives in Biology and Medicine*; 47:552–63

[6] Aliverti, V., Bonanomi, L. and Giavini, E. 1980. Hydroxyurea as a Reference Standard in Teratological Screening:Comparison of the Embryotoxic and Teratogenic Effects Following Single Intraperitoneal or Repeated Oral Administrations to Pregnant Rats,In:Further Studies in the Assessment of Toxic Actions. *Arc Toxicol Suppl*; 4: 239-247.

[7] Asano, Y. and Okaniwa, A. 1987. In utero morphological effects of hydroxyurea on the fetal development in Sprague-Dawley rats. *Jikken Dobutsu*; 36: 143-9.

[8] Asano, Y., Ariyuki, F. and Higaki, K. 1983. Behavioral Effects of Hydroxyurea Exposure During Organogenetic Period of Rats. *Congen Anom*; 23: 279-289.

[9] Brunner, R. L., McLean, M., Vorhees, C. V. and Butcher, R. E. 1978. A comparison of behavioral and anatomical measures of hydroxyurea induced abnormalities. *Teratology*; 18: 379-84.

[10] Platzek, T. and Schwabe, R. Combined prenatal toxicity of 6-mercaptopurine riboside and hydroxyurea in mice. 1999. *Teratog Carcinog Mutagen*; 19: 223-32.

[11] Yan, J. and Hales, B. F. 2005. Activator protein-1 (AP-1) DNA binding activity is induced by hydroxyurea in organogenesis stage mouse embryos. *Toxicol Sci*; 85: 1013-23.

[12] Evenson, D. P. and Jost, L. K. 1993. Hydroxyurea exposure alters mouse testicular kinetics and sperm chromatin structure. *Cell Prolif*; 26: 147-59.

[13] Hansen, D. K., Grafton, T. F., Cross, D. R. and James, S. J. 1995. Partial attenuation of hydroxyurea-induced embryotoxicity by deoxyribonucleotides in mouse and rat embryos treated in vitro. *Toxicology In Vitro*; 9: 11-9.

[14] Wilson, J. G., Scott, W. J., Ritter, E. J. and Fradkin, R. 1975. Comparative distribution and embryotoxicity of hydroxyurea in pregnant rats and rhesus monkeys. *Teratology*; 11: 169-78.

[15] Warner, C. W., Sadler, T. W., Shockey, J. and Smith, M. K. 1983. A comparison of the in vivo and in vitro response of mammalian embryos to a teratogenic insult. *Toxicology*; 28: 271-82.

[16] ClinicalTrials.gov. 2007. Hydroxyurea to Prevent Organ Damage in Children With Sickle Cell Anemia. Available at http://www.clinicaltrials.gov/ct/show/NCT00006400.