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June 17, 2004

Dr. Michael Shelby, Director
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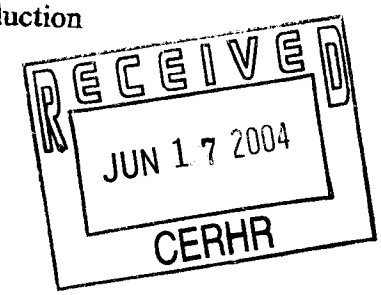

3 pages via electronic mail and fax: 919-316-4511

Dear Dr. Shelby:

The following comments are submitted on behalf of the 800,000 members and supporters of People for the Ethical Treatment of Animals (PETA) in response to the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) report on the reproductive and developmental toxicity of fluoxetine, which was made available on April 19, 2004. Public comments on the report were solicited in the *Federal Register* on April 29, 2004 (vol. 69, no. 83, pp. 23517-23518).

Fluoxetine is better known as Prozac®, since it is marketed under this and several other trade names. Based on the response received on June 16 to our Freedom of Information Act request, fluoxetine was nominated for further study by a single, anonymous individual and "no reason for nomination [was] provided." This is completely contrary to the procedure for nominations outlined on the NTP's website at http://cerhr.niehs.nih.gov/nominate/index.html.

The Recommended Animal Tests Are Unjustifiable and Unnecessary

The report concluded that additional mammalian studies are necessary in the following areas (p. 138):

(i) Rodent toxicity (using studies that comply with the current testing guidelines)
(ii) Developmental behavioral neurotoxicity, including brain histology
(iii) Effects of prenatal exposure on hippocampal development
(iv) Effects on semen quality
(v) Effects on ovulation, conception, and abortion

We cannot estimate how many animals will suffer and die in the course of these studies, but the number will undoubtedly be large. Furthermore, some of the studies for areas (ii) and (iii) will almost certainly be carried out on primates, since the behavioral effects of neurotoxicity and the emergence of the hippocampus from the archipallium are more pronounced in primates than in other mammals. In addition, neurotoxicity studies are often particularly cruel, as animals are often subjected to stressful and abusive practices, such as electric shock, food/water deprivation, and the deliberate infliction of pain or anxiety (OECD, 2000), in crude attempts to measure motor, sensory, cognitive, and other functional parameters, many of which bear little resemblance to neurological assessment methods used clinically in humans (Anger, 1990). Many common neurotoxicity tests rely heavily on measures of the animals' behavior, rather than other,

more objective physiological measures, which has raised concerns about the potential for extreme variability in test results and the subjectivity of their interpretation (Claudio et al, 2000; Tilson, 1995; Gerber and O'Shaughnessy, 1986). In fact, one EPA scientist has acknowledged that "the outcome of a study can depend on the inherent variability of a test measure" (Tilson, 2000).

Human Data Are Available and More Appropriate

Further testing on animals for fluoxetine is not only unnecessary, it is immoral, since human data are so readily available and will be much more applicable to the endpoints that the NTP wishes to study. The U.S. development program for this drug involved the full set of animal experiments required by the Food and Drug Administration (FDA), and equivalent development programs were followed in all major industrialized countries. All required clinical (i.e., human) studies were also carried out. Since its U.S. launch 17 years ago in 1987, fluoxetine has been administered worldwide to tens of millions of patients from almost every demographic group, and it has become the most widely prescribed antidepressant.

The diversity and sheer number of people who take this drug have provided Eli Lilly and other interested parties with an ideal opportunity to carry out large-scale Phase-IV (post-marketing) studies on its side effects. If all necessary data on the human effects of fluoxetine have not been obtained from such studies, this would represent a case of astonishing negligence.

The report states that additional data are needed in several specific areas. The effects on semen quality and ovulation should be investigated by studies on adult males and adult, non-pregnant females, who compose the overwhelming majority of the patients to whom fluoxetine is administered (i.e., an enormous number of patients). Investigation of the effects on conception, abortion, and developmental neurotoxicity would require studies on children and/or pregnant women. However, despite the concerns that have been raised, fluoxetine has been, and continues to be, widely administered to these groups, and there is, therefore, no reason that the necessary information could not be obtained by means of data analyses from human studies.

With regard to developmental toxicity, the report acknowledges that the principal developmental toxicity data deficiency results from the failure to maintain long-term follow-up to the studies that have been carried out (p. 136). It is also arguable that sufficient developmental toxicity data are already available to justify the decision that fluoxetine should not be administered to pregnant women or women who have the potential to become pregnant, as it is known to result in a deterioration of neonatal adaptation (p. 136). Finally, the statement that rodent data are needed from studies that comply with the current guidelines is not explained; nowhere else in the report is the failure of previous studies to meet the guidelines mentioned. It is important to stress that animal data are widely known to be of limited use for predicting side effects in humans. It is therefore incomprehensible that the NTP-CERHR believes that more experiments on thousands of animals will provide data relevant to humans that could not be obtained by statistical analysis of the real effects on millions of humans.

Conclusion

Under separate cover, we are sending you a letter regarding our concerns with the NTP-CERHR's system of test-substance nominations and solicitation of public comments. The NTP needs to explain its policy of accepting anonymous nominations, which violates the interests of open and transparent government procedures, as well as the fact that this particular nomination was pursued with "no reason for nomination provided." Both are contrary to your own instructions for nominating chemicals.

Further, the NTP-CERHR needs to assess and critique recommendations for additional animal tests and give proper consideration to possible overlap between its programs and those of other sections of the NTP and other governmental bodies. In this particular case, it is unclear what role the FDA should play in requesting additional data on Prozac.

To conclude, we strenuously object to the recommendation that large numbers of animals, whether they be rats or primates, be subjected to these experiments. We urge the NTP to state very clearly in its final report that additional animal experimentation on Prozac is not a priority and should not be pursued. While we understand that the NTP has frequently not addressed the recommended data needs in its final monographs, its failure to do so in this case would be highly irresponsible.

Sincerely,

J. Sandler

Jessica Sandler, MHS
Federal Agency Liaison

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