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FDA NATIONAL TOXICOLOGY PROGRAM LIAISON
JEFFERSON LABORATORIES NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

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Dear Dr. Masten:

On behalf of the U. S. Food and Drug Administration, I nominate acrylamide, and its principal metabolite glycidamide, to the National Toxicology Program as FDA's priority chemical nomination for Fiscal Year 2003. Under the NTP Scientific Issues Initiative, I also nominate drugs positive for QT Interval Prolongation/Induction of ***Torsade*** Proarrhythmia, under conditions of therapeutic use.

Acrylamide and Glycidamide

The presence of acrylamide in processed starchy foods first came to the attention of the FDA on April 24, 2002, when researchers at the Swedish National Food Administration and Stockholm University reported finding acrylamide in a variety of fried and oven-baked foods. The presence of acrylamide in such foods was associated with standard high-temperature cooking processes used in their preparation. Subsequent to the Swedish report, the FAO/WHO scheduled a Consultation on the Health Implications of Acrylamide in Food on June 25-27, 2002 in Geneva, Switzerland. The FAO/WHO conclusions recognized the potential carcinogenic risk to the general public from consumption of starchy fried and baked foods containing acrylamide, and listed several research areas that should be investigated (Attachment 1). Since the Swedish report, similar findings have been reported by Norway, the United Kingdon, Switzerland, Japan, and by the FDA.

It is known that following oral administration to rodents, absorption and elimination of acrylamide is rapid and distribution to tissues is extensive. Acrylamide is converted to a reactive epoxide metabolite, glycidamide, primarily through the action of the CYP 2E1 isozyme. The elimination half-life for glycidamide is slightly shorter than that for acrylamide. Both acrylamide and glycidamide react with nucleophilic amino acids in hemoglobin, notably the N-terminal valine and cysteine residues, reactions that have been used for assessing internal exposures in rodents and humans. In addition, both form glutathione conjugates that are excreted in the urine as mercapturic acid derivatives in rodents and humans. Glycidamide and acrylamide form hemoglobin adducts in rodents at ratios (acrylamide to glycidamide) similar to those observed in humans, which suggests that rodents are appropriate models for assessing exposures to glycidamide derived from acrylamide metabolism. Moreover, both acrylamide and glycidamide react with DNA (glycidamide much more rapidly) to form DNA adducts. While acrylamide is listed as 'reasonably anticipated to be a human carcinogen' in the NTP's Report on Carcinogens, the FDA requires a properly designed (dose response considerations and accounting for the food matrix through which humans are exposed), well-conducted, GLP-compliant bioassay. Results from such studies will provide the agency with sound scientific data by which more accurate risk assessments can be conducted (Attachment 2). Additional information on acrylamide may be found at the FAO/WHO Acrylamide in Foods Network, http://www.acrylamide-food.org.

The FDA held a federal interagency acrylamide meeting at FDA's Center for Food Safety and Applied Nutrition in College Park, Maryland on September 24, 2002 to review ongoing research initiatives, to provide suggestions regarding bio-monitoring, and to identify research gaps. Results from those discussions supported the FDA plan to nominate both acrylamide and glycidamide to the NTP for extensive toxicological testing (Attachments 3 and 4). The agency also held a public meeting on September 30, 2002 to solicit public comments and to present the FDA action plan for acrylamide. Public comments also supported the FDA Acrylamide Action Plan. Transcripts and slide presentations from that meeting can be viewed at http://www.cfsan.fda.gov/~dms/acryagen.html [Center for Food Safety and Applied Nutrition contact person: Dr. Richard A. Canady].

Drugs Positive for QT Interval Prolongation / Induction of *Torsade* Proarrhythmia

QT interval prolongation and an associated severe life-threatening ventricular arrhythmia, ***torsade de pointes***, is a high priority cause for concern in drug development and regulatory safety evaluation. Of the drugs recently removed from the U.S. market, one of the most common causes has been QT interval-related cardiac toxicity. For example, the non-sedating antihistamines, Terfenadine and Astemizole, and the pro-kinetic agent, cisapride, were removed from the U.S. market because of this cardiac toxicity. Additionally, the non-sedating antihistamine, Ebastine, and the antipsychotic agent, Sertindole, were denied access to the U.S. market for this reason. Finally, the antipsychotic agent, Ziprasidone, and the fluoroquinolone antibiotic, Moxifloxacin, two new drugs that prolonged QT interval in clinical trials, are labeled with severe warnings for this toxicity. Clearly, this cardiac toxicity cuts across therapeutic indications, and is therefore a general problem in drug development. Additionally, in the majority of the above cases, this cardiac toxicity was discovered either after approval during clinical use or in late stage clinical trials rather than in early drug development, with significant resultant difficulties.

Given the medical and economic consequences of this issue, the International Conference on Harmonization established an Expert Working Group to draft guidance recommending the incorporation into drug development of preclinical models predictive of QT interval prolongation and proarrhythmia. This draft guidance, ICH S7B, was signed as a Step 2 draft document in February 2002, and published for comment in the Federal Register in June, 2002 (Attachment 5). ICH S7B recommends a testing strategy comprised of both ***in vitro*** and ***in vivo*** assays considered likely to be predictive for drug-induced QT interval prolongation and proarrhythmia. Among these assays is an ionic current assay previously shown to be sensitive to known QT prolonging and proarrhythmic drugs, a ventricular repolarization assay that integrates on a cellular level test agents' effects on several ionic currents, and a conscious canine model that integrates test agents' effects on a whole animal level. These models, while likely to be predictive for QT interval prolongation and proarrhythmia, have not been rigorously evaluated for their predictability. The general consensus is that the dog is likely the best ***in vivo*** model but we do not have the data to sufficiently anchor its performance against drugs that we have had clinical experience with.

To address this deficiency, ILSI/HESI, with support from PhRMA and FDA, is evaluating the sensitivity and specificity of the ICH S7B recommended ***in vitro*** ionic current and ventricular repolarization assays, and an ***in vivo*** conscious canine telemetry model embraced by the pharmaceutical industry. Test agents to be evaluated in this exercise include non-antiarhythmic drugs that are clearly positive for QT interval prolongation and proarrhythmia in humans, as well as those considered to be clearly negative for these liabilities under conditions of clinical use. However, ILSI/HESI is evaluating only a limited subset of non-antiarhythmic drugs (those that are off patent and/or not presently marketed) recommended to be tested by FDA. The FDA can not require that sponsors evaluate the performance of their products in these model systems using problematic drugs that are presently marketed, since the risk is already known from clinical data and FDA does not have the regulatory authority to require preclinical testing under such conditions. The FDA also does not have the regulatory authority to require preclinical testing of non-problematic, negative control drugs. The level of clinical risk of QT prolongation and arrhythmia is fairly well accepted for the list of drugs named below. For those agents that are still marketed the regulatory judgement is that benefit outweighs risk when appropriate product labeling is provided for prescribing physicians to make decisions on a patient-by-patient basis. How these agents will compare to one another in a single set of well-designed test models using a shared protocol has not been investigated. A critical data gap exists in our knowledge of how well the ***in vivo*** dog model will perform in its ability to discriminate problematic from non-problematic agents and the transitional gray area between.

To fill these data gaps, the FDA recently collaborated with Georgetown University to evaluate several remaining torsadogenic drugs on the FDA lists. Due to priorities and economics, FDA/Georgetown chose to evaluate these drugs in the ionic current assay considered likely to be predictive for QT interval prolongation and proarrhythmia rather than in the more costly ***in vivo*** model. These data are available and are a useful complement to the ILSI/HESI data initiative, but have not yet been published. While the ***in vitro*** tests are clearly capable of identifying hazard potential, they are less capable of evaluating risk. For example, it is difficult to correlate ***in vitro*** and ***in vivo*** concentrations, only the parent compound is evaluated ***in vitro***, and ***in vitro*** exposure times are limited compared to ***in vivo*** exposures. In contrast, ***in vivo*** assays, such as the conscious canine telemetry model, can be used to evaluate risk by enabling assessments of safety margins based on relative drug and metabolite exposures. ***In vivo*** assays can also consider risk in the perspective of additional concurrent toxicities and pharmacological properties of a novel test agent.

In order to address both sensitivity and specificity of an experimental model it is important to evaluate both positive and negative controls. Additionally, the broadest range and most complete set of test agents should be evaluated to minimize error and bias. Finally, since results of the preclinical assays will influence the extent and design of clinical evaluation of drugs for QT interval prolongation, FDA believes it important to know whether the suggested nonclinical assays would detect drugs that have been shown to prolong QT interval in clinical trials, but for which clear evidence of proarrhythmia is lacking.

Consequently the FDA requests that the NTP evaluate both problematic and non-problematic drugs in the conscious, canine telemetry model, in order to better establish the sensitivity and specificity of this ***in vivo*** model system for evaluating the property of a test agent to prolong QT interval at relevant exposures in humans. Unlike other proposals previously nominated by FDA to NTP, in this proposal the FDA requests that a model system, namely the conscious canine telemetry model, be more rigorously evaluated using various drugs named below. The FDA is in significant need of a clearer definition of the strength and limitations of this model and future performance characteristics with unknown candidates, rather than more insight into the safety concerns ***per se*** of the listed compounds [Center for Drug Evaluation and Research contact person: Dr. Frank D. Sistare].

William T. Allaben, Ph.D., F.A.T.S.
Associate Director for Scientific Coordination
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Attachments

1. Summary Report, FAO/WHO Consultation on the Health Implications of Acrylamide in Food, June 2002
2. Introduction to the Environmental Toxicology of Acrylamide
3. Acrylamide Nomination Dossier, Oct 30, 2002
4. Summary of Discussions from Breakout Groups
5. Federal Interagency Acrylamide Research Meeting, Summary and Research Needs, September 2002
6. Draft ICH Consensus Guideline, Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (Qt Interval Prolongation) by Human Pharmaceuticals

Attachment 1
ummaryreportFina
.pdf

Attachment 2
"Acrylamide
Intro.doc"

Attachment 3
dossier-acrylamide
10-30-02.do...

Attachment 4
SUMMMARY OF
SCUSSIONS OF BRI

Attachment 5
MEETING SUMMARY
AND RESEARCH N..

Attachment 6
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