To: Richard.Irons@UCHSC.edu <Richard.Irons@UCHSC.edu>
From: Dr J. Rice <rice@iarc.fr>
Cc: George Woodall <Woodallg@api.org>
Bcc:
Sent Date: 2001-08-07 08:32:52 GMT
Subject: RE: review of research protocol

Dear Rich,

I attach a modified version of my comments from which I have deleted all references to Otto's proposal. Let me know if this suits your needs; I'm willing to add to it if that is necessary.

--Jerry

At 02:12 AM 8/7/01 -0600, you wrote:
>Dear Jerry,
>
>My IRB will not review the design of Otto's case control study (AML/NHL) >other than the differential diagnoses and patient sampling, which is my >responsibility. They will review the disease progression and molecular >epidemiology studies. They will, of course, review informed consent issues >which are being reviewed by a separate ethics panel. However, they >traditionally focus on the scientific merit as well. I didn't want to >confuse them with suggestions for changing the case control study when they >will not see it. I was suggesting that you delete specific references to >Otto's study but not that you extensively re-organize your comments. I >look forward to seeing you in September.
>
>Thanks,
>
>Rich
>
>> ----------
>> From: Dr J. Rice
>> Sent: Tuesday, August 7, 2001 12:55 AM
>> To: Dr R. Irons
>> Cc: woodallg@api.org
>> Subject: review of research protocol
>>
>> Dear Rich,
>>
>> George Woodall forwarded to me your request for separate reviews of
>> your
>> own projects.
>>
>> I did originally make a deliberate effort to integrate my review of
>> your
>> protocols and Otto's because I interpreted the charge to reviewers as
>> requiring an overall critique of the entire program, and few specific
>> instructions were given. I will be glad to separate out the parts that
>> refer to your protocols as a separate document if that will assist you,
>> but
>> before I do that it would be helpful to me to know more about the precise
>> purpose such a separate document will serve. If it is to go to a

>> University of Colorado IRB, won't it be more important for the report to
>> deal with issues other than technical ones, like informed consent? I
>> didn't address such issues in my overall review, but could add them if it
>> is necessary.
>>
>> Please inform me exactly what your IRB will be looking for and I
>> will
>> construct my separate review to address those concerns.
>>
>> I look forward to seeing you again in Chicago on September 27.
>>
>> --Jerry Rice
>>
>>
>> Jerry M. Rice, Ph.D.
>> Chief, Unit of Carcinogen Identification and Evaluation
>> International Agency for Research on Cancer
>> 150 cours Albert Thomas
>> 69372 Lyon Cedex 08
>> FRANCE
>>
>> tel: (+33) 4 72 73 84 76
>> fax: (+33) 4 72 73 83 19
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>

Attachments:

ATT05658.txt
Review of API Grant Proposal Univ CO Irons.doc

REVIEW OF API-SPONSORED BENZENE HEALTH EFFECTS PROTOCOLS

Reviewer: Jerry M. Rice, PhD
International Agency for Research on Cancer
Lyon, France

Date: 19 July 2001

Project title: Benzene Health Research Project, Shanghai, China

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OVERALL COMMENTS

The Benzene Health Research Project (hereafter, the Project) is an ambitious and complex program. Component studies are well thought out and have the potential to clarify several important issues concerning the carcinogenic risks of exposures to benzene. Study populations in the People's Republic of China (PRC) are extremely appropriate for the investigations that are proposed. The principal investigators are very well qualified to carry out the various aspects of the proposed studies.

Chinese practice in writing names is to give the family name first and the personal name second, just the reverse of American practice. Whichever practice is followed in this Project should be clearly stated and then adhered to uniformly by all investigators. Bibliographic citations can become badly confused if family names are mistaken for personal names, and vice versa.

Criteria for diagnosis and classification of lymphoid and myeloid neoplasms and related conditions have been in a state of rapid evolution for many years. Hematologists have only recently achieved international consensus on a reasonably comprehensive classification system for these conditions (1,2) which have now been incorporated into the most recent (third) edition of the International Classification of Diseases for Oncology (ICD-O) (3). It is absolutely essential for the success of the Project that the current classification system be used throughout, in all three studies, and that the underlying concepts be incorporated into the analysis of data. This is especially true for those categories of lymphoid neoplasms where it is now recognized that there are both leukemic and lymphomatous clinical presentations of what is fundamentally the same disease, and that separate tabulation of leukemias and lymphomas is not appropriate. This issue is touched upon further under **SPECIFIC COMMENTS**.

A relatively minor but highly visible change introduced in the third edition of ICD-O is replacement of the possessive form in nomenclature that involves names of individuals. "Hodgkin's disease," for example, is now "Hodgkin

lymphoma (Hodgkin disease)" and use of this revised spelling would clearly send a signal to readers that the most up-to-date system of classification is being followed.

SPECIFIC COMMENTS

Protocol I: Analysis of disease progression for aplastic anemia, myelodysplastic syndrome, acute myelogenous leukemia and benzene poisoning in Shanghai, China (Principal Investigators: Richard D. Irons and Hua Fu)

The background, scientific and ethical issues, and specific technical approaches to be used are very well presented and the statement of specific goals is clear and reasonable. The discussion of potential confounders is excellent.

The discussion of classification of myeloid and lymphoid neoplasms is excellent. The summary of the FAB and WHO classifications and the way the two will be used in this Project is very lucid. It would be desirable to add a reference to ICD-O (third edition), into which the WHO classification system described by Dr Irons has been incorporated. ICD-O (third edition) is now the standard to which cancer registries worldwide will adhere, and it should also be the standard for international research projects like this one.

One matched hospital-based control is to be selected for each case of aplastic anemia, myelodysplastic syndrome or acute myelogenous leukemia and for each referred case of benzene poisoning. Is this enough? Would conclusions be strengthened by having two or more controls for each case? Some discussion of this question is desirable.

Protocol II: Molecular epidemiology of benzene-exposed workers in Shanghai, China (Principal Investigators: Richard D. Irons and Hua Fu)

[Pagination changes on my copy after page 117 and begins again with page 107.]

The choice of metabolic activities to be quantified is reasonable, but necessarily represents a choice among many alternatives and may need to be revised during the study. It needs to be remembered that there is no convincing evidence from intensive dosing studies in animals that hydroquinone or quinone are carcinogenic at any organ site. Metabolism <u>in situ</u> may be essential for the toxicity and carcinogenicity of benzene in the bone marrow.

Identification of benzene metabolites in bone marrow (specific aims 3 & 5; pages 109, 114) is very ambitious. The feasibility study that is to be carried out (page 136) is not described in detail. Some indication of what levels of free and

bound benzene metabolites can be detected in any tissues in animals after benzene dosing would be informative. More discussion of the feasibility of this aspect of the study is desirable.

REFERENCES

1. Harris NL *et al.* (1999) World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November 1997. *J. Clin. Oncol.* **17**: 3835-3849

2. Harris NL *et al.* (1999) World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November 1997. *Annals Oncol.* **10**: 1419-1432

3. Fritz A., Percy C., Jack A., Shanmugaratnam K, Sobin L., Parkin D.M. & Whelan S., Eds. (2000) *International Classification of Diseases for Oncology (Third Edition).* World Health Organization, Geneva

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The Benzene Health Research Project (hereafter, the Project) is an ambitious and complex program. Component studies are well thought out and have the potential to clarify several important issues concerning the carcinogenic risks of exposures to benzene. Study populations in the People's Republic of China (PRC) are extremely appropriate for the investigations that are proposed. The principal investigators are very well qualified to carry out the various aspects of the proposed studies.

At the moment the Project consists of three parts: two thoroughly detailed and interrelated research proposals (protocols I and II) and a third proposal that is provided as a draft. It would facilitate review of this Project if an overall introduction were provided that would serve to integrate its different components. This is especially important since both Dr Irons' protocol I and Dr Wong's proposal refer to "the case control study," but each of these investigators seems to mean his own independent investigation. Some designations are needed for the two projects that will be used by both P.I.s, to avoid confusion.

Such an introduction should also clearly define the composition and roles of the review body or bodies that will undertake initial review of proposals and provide oversight during the conduct of the studies. One of the project descriptions refers to an External Scientific Advisory Board (protocol I, p. 24) and a Scientific Review Panel (protocol I, p. 25), but these designations are somewhat different from those used in other documents.

As all three projects will depend on the same diagnostic laboratory, which is to be established in Shanghai by local staff trained at or by the University of Colorado, considerable coordination will be required for the successful conduct and effective presentation of these studies. It is more clear from protocol I than from Dr Wong's proposal how this will be done. This aspect of the current documents could be improved. This reviewer had to expend some time and

effort to discover exactly how protocols I/II and the diagnostic laboratory that will be created in support of those protocols are related to Dr Wong's study.

Chinese practice in writing names is to give the family name first and the personal name second, just the reverse of American practice. Whichever practice is followed in this Project should be clearly stated and then adhered to uniformly by all investigators. In the current documents, clearly both conventions are used (e.g., Hua Fu (protocol I, page 2) but Fu Hua (Wong & Hua draft, cover page). Bibliographic citations can become badly confused if family names are mistaken for personal names, and vice versa.

Criteria for diagnosis and classification of lymphoid and myeloid neoplasms and related conditions have been in a state of rapid evolution for many years. Hematologists have only recently achieved international consensus on a reasonably comprehensive classification system for these conditions (1,2) which have now been incorporated into the most recent (third) edition of the International Classification of Diseases for Oncology (ICD-O) (3). It is absolutely essential for the success of the Project that the current classification system be used throughout, in all three studies, and that the underlying concepts be incorporated into the analysis of data. This is especially true for those categories of lymphoid neoplasms where it is now recognized that there are both leukemic and lymphomatous clinical presentations of what is fundamentally the same disease, and that separate tabulation of leukemias and lymphomas is not appropriate. This issue is touched upon further under **SPECIFIC COMMENTS**.

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The planning of these studies is at a stage where a direct meeting of investigators and reviewers for discussion and clarification of specific issues would be productive.

SPECIFIC COMMENTS

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The background, scientific and ethical issues, and specific technical approaches to be used are very well presented and the statement of specific

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Case-control studies of acute non-lymphocytic leukemia and non-Hodgkin['s] lymphoma in Shanghai (Co-investigators: Otto Wong & Fu Hua) **(DRAFT, 6-26-2001)**

Will the 500 cases of ANLL <u>all</u> expected be from among the 600 or so AML cases expected to be enrolled in protocol I during its 5 years of recruitment?

It would be helpful to have more precise cross-referencing between this study and protocol I.

The text (p. 8) specifies that blood diseases to be considered in selecting controls will be classified according to the ninth edition of the International Classification of Diseases (ICD). This edition is now outdated in many respects and has been superseded by the tenth edition of the ICD and by the third edition of ICD-O. This reference should be changed and updated, as recommended in **OVERALL COMMENTS**.

Section 2.10 on data management and confidentiality (pages 12-13) is very difficult to read. Especially, the allusions to disease progression studies apparently refer to protocol I (Irons and Hua). In protocol I it is clearly stated that AML cases will not be part of the disease progression study since AML is the ultimate disease in the sequences. This section needs to be clarified.

Since B-cell lymphoma/leukemia will be an end-point in this investigation, it is essential to identify all possible confounders (cf. protocol I). The concern that is expressed (page 10) for possible embarrassment of participants in the study could be badly misplaced, given the importance of certain STDs as confounders and the explosion of HIV prevalence that is now occurring in the PRC, although until very recently this has not been "officially" acknowledged. This aspect of the study needs further discussion during the scientific review meeting that is to be scheduled during this summer.

REFERENCES

1. Harris NL *et al.* (1999) World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November 1997. *J. Clin. Oncol.* **17**: 3835-3849

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