A PROPOSAL FOR

A CODE OF

GOOD EPIDEMIOLOGICAL

PRACTICE

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A Code of Good Epidemiological Practice

1.0 Purpose

With the emergence of epidemiology as a distinct discipline and the proliferation of scientists engaging in various forms of epidemiological research, the establishment of minimum standards of practice has assumed increasing importance. While every epidemiological study that is undertaken will have unique aspects, certain principles should guide investigators in designing studies; recruiting and interacting with study participants; collecting and managing study data; interpreting and communicating study results; and archiving study materials for future use. In particular, the establishment of minimum standards should improve the quality and consistency, and thus enhance the credibility, of epidemiological research.

The European Data Protection Directive, which was adopted in late 1995, provides an important additional reason for embracing a code of good epidemiological practice [Directive 95/46/EC, 1995 O.J. (L281) 31]. Most if not all countries within the European Union will be required to enact national data protection legislation or to revise current national legislation in response to the European Data Protection Directive. This *Code* has been designed to facilitate compliance with the requirements for the handling of personally identifiable information that can be expected to prevail within the European Union for the foreseeable future as a result of the European Data Protection Directive.

It is critical that data protection legislation permit competent, professional researchers to undertake well-designed studies on health issues using techniques involving the collection and analysis of personal data. Researchers also must acknowledge, however, that the European Data Protection Directive makes access to sensitive personal data a privilege available only when the study in question appears likely to have sufficient merit to outweigh any associated risks to personal privacy. As a consequence, epidemiologists must be prepared in the future to accept responsibility for the way in which their studies are planned, conducted, analysed and reported in order to ensure the maximum benefit to society.

The relatively strict regulatory environment contemplated by the European Data Protection Directive has implications for researchers outside as well as inside the European Union. The reason is that it soon will be illegal for anyone within the European Union to share personal data with anyone outside the Union unless (1) the country to which data will be transferred has adopted data protection legislation that is deemed to be "adequate" or (2) the recipient of the data otherwise provides "adequate" assurances that the data will be handled in accordance with European Union standards. Moreover, the European Data Protection Directive requires the European Commission to enter into negotiations with non-Union countries looking toward the adoption of data protection practices comparable to those being adopted by members of the European Union.

This *Code of Good Epidemiological Practice* represents the most comprehensive effort to date to establish minimum practice standards within the field of epidemiology. Codes of practice have been followed for a number of years in related fields, as evidenced by the guidelines for good clinical and laboratory practice that have been adopted in the United States, the European Union and Japan. [*See, e.g.*, International Conference on Harmonization, Topic E6, Guideline for Good Clinical Practice, CPMP/ICH/135/95 (1996).] In addition, a document entitled Guidelines for Good Epidemiological Practice was developed several years ago by the Chemical Manufacturers Association in the United States. [Epidemiology Resource and Information Center (ERIC) (1991).] This *Code* builds upon those related efforts while responding, as noted, to the new challenges and opportunities presented by the European Data Protection Directive.

The provisions of this *Code* have been designed to be enabling rather than onerous. Although establishing minimum standards of practice in a number of critical areas, this *Code* does not contain a formula or set of formulas for epidemiological research. Neither will this *Code* prevent epidemiologists from exercising a full range of creativity and innovation in study design and analysis. At the same time, and for the reasons just noted, compliance with this *Code* will not guarantee the validity of a study or its conclusions. These, as always, can be evaluated only by appropriately trained and experienced epidemiologists.

This *Code* should be useful to a range of individuals and institutions. The *Code* was designed, of course, to be used by those conducting epidemiological research under the European Data Protection Directive. Data protection officials also should find the *Code* to be useful in evaluating study proposals that call for the collection of personal data. For those newly entering the field of epidemiology, either as a student or as an established scientist from another field, the Code provides a useful description of the minimum level of accountability that is expected.

Finally, it is anticipated that the *Code* will be helpful to end users of epidemiological studies, including policy makers, research sponsors and risk assessors. Although compliance with the provisions of this *Code* will not put an end to debates concerning the meaning of epidemiological results or conclusions, this *Code* should be of value in determining whether particular studies have met minimum standards of epidemiological practice.

2.0 Scope and Application

This *Code* applies to all epidemiological investigations, regardless of sponsor, including --

- observational studies utilizing case-control or cohort methodologies; cross-sectional studies; ecological studies; surveillance studies; feasibility, pilot and prioritization studies; cluster investigations; methodological studies; and
- intervention studies, to the extent not covered by existing standards of good clinical and/or laboratory practice.

The provisions of this *Code* apply to all phases of covered research, including protocol development and approval, conduct of the investigation, interpretation and reporting of findings, and archiving of study materials.

This *Code* is not intended to apply to clinical trials, which are governed by separate standards of good clinical and/or laboratory practice.

Commentary:

Broad application of the standards set forth in this Code should enhance the reliability, reproducibility, transparency and consistency of epidemiological research while ensuring that personal data are properly utilized and protected. The privacy rights and interests of research subjects can be compromised as seriously in the course of a feasibility study as in a full-scale investigation. Further, the public has a direct and immediate interest, which is shared by practising epidemiologists as well as study sponsors, in ensuring that all epidemiological studies meet or exceed the standards set forth in this Code. Epidemiological studies not meeting or exceeding these standards generally should not be undertaken.

Businesses and institutions regularly engage in activities that are not formal epidemiological studies but have many of the earmarks of such studies. For example, a company might gather employee health data on a periodic basis and perform statistical analyses designed to detect patterns in the data. In general, such health-data monitoring should be conducted in accordance with this Code to the extent reasonably practicable. At the same time, however, steps can be taken in such circumstances to reduce the burden that compliance with this Code otherwise might present. Thus, for example, a company that engages in periodic health monitoring should consider preparing a generic protocol that identifies the data to be gathered and the analyses to be performed.

This Code does not apply to clinical studies. The reason is that most such studies are covered by other standards documents, including in particular codes of good clinical and laboratory practice, the purposes of which are similar to those of this Code. Some studies -- often referred to as intervention studies -- involve clinical/experimental as well as epidemiological phases. This Code should be followed during the epidemiological

phases of such a study (i.e., the gathering and analysis of baseline and post-intervention data) and also should provide some guidance in connection with the experimental phase(s) (e.g., the assignment of study participants to treatment regimens).

An expert working group convened by the International Life Sciences Institute developed and published in 1995, as part of a cooperative agreement with the U.S. Environmental Protection Agency, a set of standards to guide the use of meta-analytic techniques in the investigation of environmental health issues [Blair 1995]. Compliance with those or a similar set of standards is recommended for any meta-analysis or other comparable inquiry that is undertaken.

On rare occasions a study must be conducted according to an abbreviated schedule because of an urgent need to investigate a sudden and serious threat to public health. Under those circumstances, full compliance with this Code may not be possible. Nevertheless, the spirit of the Code should be respected. Indeed, as one proponent of a code of good epidemiological practice recently observed, during a public health emergency a clear set of standards can help epidemiologists and others ensure that steps that are important to the reliability of the research are not overlooked [Tirey 1996].

3.0 Definitions

For the purposes of this *Code*, the terms listed below have the definitions provided:

3.1 **Anonymisation** - the process by which data relating to natural persons are placed in a form in which it is not possible to identify directly or indirectly the persons to whom they relate.

3.2 **Clinical study** - an experiment in which different treatments are provided, usually by randomized allocation, for the purpose of determining whether a particular treatment is associated with a change in health status.

3.3 **Comprehensive final report** - a full description of an epidemiological study prepared at the conclusion of the study containing all of the information required by Section 8.1 of this *Code*.

3.4 **Data protection** - has the meaning provided by the applicable national law. Whenever no such law is in effect, *data protection* means the process of safeguarding *personal data* to ensure that it is processed in accordance with the provisions of the *European Data Protection Directive*.

3.5 **Data protection official** - a person appointed by the *principal investigator* to ensure that applicable *data protection* procedures are followed.

3.6 **Disseminate** - to report the findings, results and/or conclusions of an *epidemiological study*, either orally or in writing.

3.7 **Epidemiological study** - any research relating to the distribution and determinants of health-related states or events in specified populations.

3.8 **European Data Protection Directive** - refers to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995, 1995 O.J. (L281) 31, on the protection of individuals with regard to the collection and *processing* of *personal data* and on the free movement of such data.

3.9 **Exploratory analysis** - analysis of a data set without a predetermined hypothesis, sometimes referred to as a descriptive study. An *exploratory analysis* can be used to generate hypotheses, to suggest the most appropriate analytical techniques, to set priorities for future research and/or to help focus subsequent analyses.

3.10 **Identifiable person** - one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his or her physical, physiological, mental, economic, cultural or social identity.

3.11 Intervention study - a study designed to test a postulated relationship between health-related states or events in a specified population and other characteristics of that population by modifying at least one of those characteristics.

3.12 Peer review - the process whereby *protocols* and *reports* are judged for technical and scientific merit by other experienced scientists in the same or related fields.

3.13 Personal data - information relating to an identified or *identifiable* natural person.

3.14 Principal investigator - the member of the *research team* who has ultimate responsibility for the design, conduct, analysis, interpretation, *reporting* and documentation of an *epidemiological study* as well as for the selection and preparation of *study materials* for archive purposes.

3.15 Processing data - any operation or set of operations that is performed upon data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration; retrieval; consultation; use; disclosure by transmission, dissemination or otherwise making available; alignment or combination; blocking, erasure or destruction.

3.16 Protocol - the document or documents providing full technical details concerning the proposed design, conduct, analysis, interpretation, *reporting* and documentation of an *epidemiological study* as well as the selection and preparation of *study materials* for the archive. The *protocol* includes references to any *standard operating procedures* developed for or intended to be utilized during the study as well as any amendments to the initial *protocol*.

3.17 Quality assurance - all the planned and systematic activities implemented to provide adequate confidence that a study will fulfil requirements for quality.

3.18 Report - a presentation of the findings, results and/or conclusions of an *epidemiological study*, regardless of whether the presentation is made orally or in writing.

3.19 Research team - the individuals or entities (including *subcontractors*) contributing to the design, conduct, analysis, *reporting*, documentation or *verification* of an *epidemiological study* as well as those having responsibility for the selection and preparation of *study materials* for the archive. Persons asked to serve as independent scientific or ethical reviewers should not, as a result of such service, be considered members of the *research team*.

3.20 Sponsor - an individual or entity providing financial or other material support in connection with an *epidemiological study*.

3.21 Standard operating procedure - the description of any standard method or process for conducting or accomplishing a routine research activity, including *quality assurance* activities.

3.22 Statistical methodology - techniques by which study data are analysed and displayed.

3.23 Study materials - any documents or other materials, in whatever form, that relate to a particular *epidemiological study*, including at least those items listed in Section 10.1.

3.24 Subcontractor - an individual or entity undertaking, pursuant to a contract or other binding agreement, discrete tasks described in the study *protocol*, thus becoming a member of the *research team*.

3.25 Subject [or data subject] - an individual with respect to whom data, including *personal data*, are collected in the course of an epidemiological study.

3.26 Third country - a country that is not a member of the European Union.

3.27 Third party - an individual or entity other than the *quality assurance* auditor, the *sponsor(s)*, a member of the *research team*, a data protection official or a person or institution responsible for independent scientific or ethical review. The *data subject* is not a *third party* for the purpose of receiving access to his or her own *personal data* under Section 8.3.

3.28 Verification - the procedures carried out to ensure that the data contained in *reports* on an *epidemiological study* match original observations.

Commentary:

Section 3.0 provides definitions of significant terms used in this Code. No effort has been made to define terms that are well known to practising epidemiologists. To assist in cross-referencing, whenever a term used in a definition is itself defined in this section, the term appears in italics.

One issue concerning terminology requires elucidation. This Code employs the terms "findings," "results" and "conclusions" without attempting to define those terms or draw clear distinctions among them. The reason is that as used by researchers within the field of epidemiology, these terms overlap. The relevant provisions of this Code are meant to apply to any and all reports of the findings, results or conclusions of epidemiological studies, however those terms may be defined or used by individual investigators.

4.0 Organization and Responsibilities

For an epidemiological study to achieve its intended goals, a number of parties must work together, including the principal investigator, the other members of the research team, the subcontractors if any and the sponsor(s). Moreover, before a study proceeds, it should be subject to scientific and ethical review. While it proceeds, a study should undergo periodic monitoring by a quality assurance auditor.

4.1 Sponsorship agreement.

Whenever an epidemiological study is supported by one or more sponsors, a written agreement should be prepared that identifies the mutual rights and responsibilities of the sponsor(s) and the principal investigator. Before the study proceeds, the sponsor(s) and the principal investigator should review and sign the agreement. The sponsor is entitled to expect that the study will be undertaken as agreed in the absence of a material change in the underlying circumstances and the principal investigator is entitled to expect that any support that has been promised will be provided. Under no circumstances should the sponsorship agreement permit the sponsor(s) to control the interpretation or prevent the timely dissemination of reports on the study. Ordinarily the following points also should be addressed in a sponsorship agreement:

- the identity of the individuals or institution(s) responsible for performing independent scientific and ethical reviews and of the quality assurance auditor;
- whether the sponsor has the right to receive copies of all reports of the study;
- whether the sponsor has the right to review and comment on reports before dissemination;
- the identity of the individual(s) or institution(s) responsible for providing compensation in the event a subject suffers injury as a result of participating in the study;
- who owns materials produced in the course of the study; and
- who has responsibility for managing the study archive.

4.2 Research team relationships

To the extent possible, the responsibilities of and relationships among the members of the research team should be defined in the protocol.

4.3 Research team expertise

The principal investigator, with advice from independent scientific reviewers (*see* Section 4.7), should ensure that the research team as a whole possesses expertise in all of the fields covered by the protocol and that members of the research team have the education, training and/or experience needed to perform in a professional and competent manner any tasks assigned to them in the study protocol. For each member of the research team, the principal investigator should have access to an up-to-date curriculum vitae.

4.4 Responsibilities of principal investigator

The principal investigator should assume overall responsibility for the design, conduct, analysis, reporting and documentation of the study as well as for the creation of the archive. If under the sponsorship agreement the principal investigator owns the study materials, the principal investigator should assume responsibility for managing the archive. The principal investigator also should assume responsibility for the scientific quality of the study and related quality control efforts. Before permitting an epidemiological study to proceed, the principal investigator should ensure that the study proposal has been approved by the persons or institutions responsible for independent scientific and ethical review and that sufficient financial resources have been committed to permit the study's timely and proper completion. Anyone proposing to act as the principal investigator for an epidemiological study should be prepared to devote sufficient time to the study to ensure that it will be undertaken in accordance with the study protocol and in compliance with this *Code* as well as with any applicable legal requirements.

4.5 Responsibilities of other research team members

Each member of the research team, including any subcontractor, has an independent and concurrent responsibility for ensuring that he/she understands the nature of the research tasks for which he/she is to be given operational responsibility, is capable of performing such tasks in a professional and competent manner and is familiar with the provisions of this *Code* as well as any applicable legal requirements.

4.6 Responsibilities of sponsor(s)

The sponsor(s) of an epidemiological study should provide financial or other material support as set forth in the sponsorship agreement and should require, as a condition of providing such support, that the study be undertaken in a manner that is consistent with this *Code* as well as with any applicable legal requirements. Ordinarily the sponsor(s) should not offer and the principal investigator should not accept research funding or other sponsorship support that is contingent upon the approval of interim or final study findings or results. If the sponsorship agreement entitles the sponsor(s) to retain ownership of the study materials, the sponsor(s) should assume responsibility for managing the archive.

4.7 Independent scientific review

In the early stage of planning an epidemiological study, individuals (not members of the research team) or institutions should be identified who/that will be responsible for independent scientific review. Those individuals or institutions should review the protocol to determine whether the proposed study design is appropriate given the study's objectives. The reviewers also should consider whether the members of the research team are qualified to undertake the proposed study. It is recommended in addition that they monitor the conduct of the study as it proceeds and review reports of study results prior to dissemination. Persons designated to perform the scientific review should be experts qualified in the disciplines covered by the protocol.

4.8 Independent ethical review

The protocol of a proposed epidemiological study should designate the individuals or institutions who/that will be responsible for performing an independent ethical review. Those individuals or institutions should ensure that the proposed study is designed in a manner that will safeguard the rights, safety and well-being of research subjects, including the rights specified by applicable data protection legislation. In particular, they should consider carefully the conclusions of the persons responsible for performing the scientific review of the proposed study and determine whether the study is of sufficient value to outweigh any loss of personal privacy. If a data protection official has been appointed, those conducting the independent ethical review should satisfy themselves regarding the qualifications of the appointee and should ensure that he/she will have sufficient power and independence to perform the duties assigned by Section 7.10. Persons or institutions designated to perform the independent ethical review should be qualified by education and experience to carry out their responsibilities. No study should be undertaken without approval from the persons or institutions responsible for the independent ethical review.

4.9 Subcontractors

The responsibilities of any subcontractor retained to assist in an epidemiological study should be set forth clearly both in the protocol and in a written agreement signed by the principal investigator and the subcontractor. The subcontractor should act in accordance with all commitments made in the written agreement and should comply with the provisions of this *Code* as well as with any legal requirements that may apply.

4.10 Quality assurance auditor

See Section 9.2.

4.11 Facilities

The principal investigator should ensure that adequate physical facilities, including office and laboratory space, relevant equipment, and office and other supplies,

have been provided to permit the members of the research team to perform the tasks assigned to them and to permit the study's timely completion. The person or institution who/that owns the study materials under the sponsorship agreement should ensure that suitable storage facilities are available to maintain research materials in a safe and secure environment in accordance with Sections 7.0 and 10.0 and with any applicable data protection legislation.

4.12 Data protection official

See Section 7.10.

Commentary:

Although some commentators have urged the establishment of a formal certification program that would attest to the qualifications of at least some of the individuals undertaking or participating in epidemiological studies, including in particular anyone acting or proposing to act in the capacity of principal investigator, a formal program does not appear to be needed at this time. The real issue -- one that is not amenable to a bureaucratic solution -- is whether the members of a research team, individually and collectively, possess the expertise that is needed to complete in a professional and competent manner the tasks assigned to them in the operative protocol. Although primary responsibility in that connection resides with the principal investigator, the study sponsor(s) as well as the persons or institutions responsible for scientific and ethical review bear an independent and concurrent responsibility for ensuring the requisite expertise.

Under this Code, the principal investigator bears primary responsibility for all aspects of an epidemiological study. In some institutional settings, the person responsible for preparing the protocol and overseeing the day-to-day conduct of an epidemiological study may be subordinate to a person with a title such as "research director" or "study director." For purposes of this Code, actual responsibilities rather than title determine whether a person is the "principal investigator." In a university setting, for example, a faculty member may serve as "research director" and may oversee a research project that is under the day-to-day control of a graduate student. In that situation, the faculty member probably would bear final responsibility for all elements of the research project and thus, for purposes of this Code, would be the principal investigator. The graduate student would be a member of the research team. Although this Code does not take a position on specific institutional arrangements, it does require that someone with appropriate authority clearly be designated the principal investigator.

In a corporate setting, the relationship between sponsor and research team may be complicated. In some cases, all members of the team may be employees of the corporation that sponsors the research. In other cases, one or more members of the team may be employees of the sponsor. The principal investigator may or may not be employed by the sponsor. Whenever members of the research team are employees of the sponsor, the sponsor is in a very real sense a participant in the research process. Regardless of

any employment relationship that might exist between them, however, the sponsor and members of the research team should fulfil their responsibilities under this Code.

The sponsor is entitled to expect that a study will be undertaken as agreed in the absence of a material change in the underlying circumstances. At the same time, the principal investigator should not be prevented from making changes in the proposed methodology whenever new scientific findings or developments materially change the circumstances underlying the original study proposal. For example, a study protocol might identify a particular device to measure the exposure of study subjects to a specified chemical in the environment. If during the course of the study a new device is developed that would increase the accuracy of exposure measurements, the principal investigator should not be prevented from using the new device simply because the older measuring device was specified in the sponsorship agreement or the protocol. Whenever the principal investigator plans to alter the study based on a material change in the underlying circumstances, he/she should amend the study protocol and obtain appropriate approvals from the sponsor(s) and others. See Section 5.13.

The primary obligation of the sponsor(s) is to provide the support promised in the sponsorship agreement. The sponsor(s) should not use the power of the purse, however, to interfere with the intellectual freedom of the research team. It is equally important that members of the research team exercise this freedom responsibly. In general, the sponsor(s) should not request and the principal investigator should not accept a sponsorship agreement that gives the sponsor(s) the right to approve interim or final results, control their interpretation or prevent the timely dissemination of research reports.

Each proposed epidemiological study should be reviewed from two distinct points of view -- i.e., scientific and ethical -- before it proceeds. Each proposed study should undergo an independent scientific review to ensure that it is scientifically sound. The scientific review should consider, among other things, whether the proposed study is consistent with principles of good epidemiological practice, including in particular the core principles described in this Code. A proposed study that is not consistent with such principles should not be allowed to go forward.

The approach to scientific review should be flexible in two respects. First, the quality of an epidemiological study generally will be enhanced if the persons responsible for scientific review are completely independent of the research team and of any institution with which the team may be affiliated. In many situations, however, both financial and institutional constraints make complete independence difficult if not impossible to achieve. Nevertheless, as a general principle the scientific review should be as independent as possible in light of all of the circumstances.

Second, the Code recommends that the persons responsible for scientific review be given an opportunity to comment on study reports before they are disseminated. That recommendation is intended to emphasize the importance of thorough, independent peer review before dissemination. In formulating his or her comments, the peer reviewer should consider, among other things, whether (a) the epidemiological study was carried out as described in the protocol; (b) deviations from the protocol have been noted and

explained; (c) all major findings have been reported; (d) any uncertainties concerning the results of the study have been reported; and (e) alternative interpretations have been discussed and critically evaluated.

After undergoing scientific review, the proposed study should undergo an independent ethical review designed to ensure that the safety, privacy and well-being of all research subjects will be fully protected. All research studies involving experimentation on human beings must comply, of course, with the most recent revision of the Declaration of Helsinki. To ensure that all subjects are treated in an ethical manner, the ethical review should evaluate the proposed study against a widely recognized code of ethical conduct such as the International Guidelines for Ethical Review of Epidemiological Studies [CIOMS 1991]. Furthermore, results of the scientific review should be made available to the persons responsible for the ethical review in order to permit them to determine whether the proposed study is of sufficient value to outweigh any loss of personal privacy. As discussed in Section 1.0, the use of personal data for scientific research is a privilege. The persons responsible for the ethical review should take full account of the privileged status of personal data before approving a proposed epidemiological study.

Many countries, companies, universities and research centres have established institutional structures for proposed scientific studies, including epidemiological studies. While the development of such institutional structures is to be encouraged, this Code does not presuppose any particular set of arrangements and is intended to apply regardless of the institutional setting. Whenever appropriate institutional structures do not exist, it is the responsibility of the principal investigator and the sponsor(s) to ensure that qualified persons who understand their responsibilities are recruited to provide independent scientific and ethical reviews before the proposed epidemiological study proceeds.

One type of review not dealt with in this Code is what in the United States has been termed "institutional" review. During this type of review, representatives of the institution(s) -- for example a company or university -- with which the principal investigator or the research team is affiliated typically focus on whether the proposed study is consistent with policies and priorities that have been established by the institution(s). The scope and substance of any such review is determined, of course, by the institution(s) concerned. Before data collection commences, any such review that may be required should be completed and any required approvals should be obtained. Institutional approval forms should be maintained in the study archive.

5.0 Protocol

The proposed study should be described in a reasonably comprehensive manner in a written protocol. Data collection should not commence prior to obtaining appropriate approvals from the persons and/or institutions responsible for independent scientific and ethical reviews as well as any necessary institutional approvals. The protocol typically should include:

5.1 a descriptive title;

5.2 an abstract of the protocol;

5.3 the names of the principal investigator and all other members of the research team, including any subcontractors, and a brief curriculum vitae for each indicating relevant education, training, skills and experience;

5.4 the identity and address of the study sponsor(s), the conditions, if any, attached to the funding and a copy of the sponsorship agreement or a draft thereof;

5.5 a statement of any potential conflicts of interest;

5.6 a statement of the objectives, including research hypotheses and the extent to which each hypothesis can be tested by the methods described in the protocol;

5.7 a proposed study timetable with milestones, including approval date, starting date, periodic progress review dates and anticipated completion date;

5.8 a description of the procedures to be followed to protect research subjects from unnecessary risk of harm, including harm to or interference with the privacy rights ensured by applicable data protection legislation (*see* Section 7.3);

5.9 a description of any residual or unavoidable risks that the research design may pose to research subjects;

5.10 a reasonably comprehensive, critical review of the relevant literature that permits others to assess the likely significance of the proposed study and to recognize potentially important methodological issues;

5.11 the results of any relevant feasibility study or, if the proposed study is a feasibility study, a description of the criteria that will be employed in deciding whether to undertake a full-scale study following completion;

5.12 a reasonably comprehensive description of the study design and the methodology to be utilized, typically including:

General

5.12.1 the overall research design and strategy (*e.g.*, exploratory analysis, cohort, case-control) and reasons for choosing the proposed design;

5.12.2 the data sources for exposure, health status and risk factors (*e.g.*, questionnaires, biological measurements, disease registries);

5.12.3 the projected study size, including where appropriate calculations of statistical power indicating the basis on which the decision concerning study size was made;

Data Collection

5.12.4 the criteria for selection of study subjects and their allocation to groups;

5.12.5 the methods and criteria that will be used in assessing health outcome(s);

5.12.6 the methods and criteria that will be used in assessing exposures or pertinent characteristics of the study population, including a justification of any qualitative and semi-quantitative methods and full details concerning sampling, analytical, validation and quality assurance aspects whenever quantitative methods are used;

5.12.7 the methods and criteria that will be used to collect information about confounders;

5.12.8 any significant limitations inherent in the methods and criteria used to assess outcomes, exposures and potential confounders;

Data Processing and Analysis and Quality Assurance

5.12.9 the statistical methodology that will be used to analyze the data, including any procedures for obtaining point estimates and confidence intervals, the procedures for defining and categorizing exposure and dose (or activity patterns) and for relating that information to the health outcome(s) being investigated and the methods for assessing and controlling confounding and for assessing possible effect modifying variables;

5.12.10 any significant limitations inherent in the study design, data sources and proposed statistical methodology;

5.12.11 a description or identification of standard operating procedures to be used;

5.12.12 a description of or reference to quality assurance, quality control and verification procedures for all phases of the study;

5.12.13 the identity of the quality assurance auditor, the data protection official, if any, and the persons and/or institutions responsible for independent scientific and ethical reviews;

5.12.14 the proposed criteria for interpreting the findings;

5.12.15 an indication of the extent to which the analysis should extend to conclusions or speculation beyond the results and to recommendations for action or further work;

Dissemination

5.12.16 whenever possible, a description of plans for disseminating reports of study findings, results and conclusions;

Protocol modifications

5.13 a description of procedures to be followed in amending the initial study protocol, documenting any such amendments and obtaining for such amendments any required sponsor approvals, institutional approvals or approvals from the relevant data protection authority as well as from the persons or institutions responsible for the independent scientific and ethical reviews;

5.14 a description of the circumstances under which the research project might be terminated prior to completion and the identity of those persons who have the authority to order a premature termination;

5.15 a description of the procedure(s) that will be used to reach agreement between the sponsor and the principal investigator concerning proposals to amend the protocol or terminate the study prior to completion;

Archiving

5.16 a description of the plan for selecting and preparing study materials for the archive and, whenever the principal investigator bears the responsibility, of the plan for creating and managing the archive, including a description of the materials to be archived (*see* Section 10.1), the length of time that materials will be held (*see* Section 10.2) and the criteria that will be employed in handling third party requests for access to such materials (*see* Sections 10.3 and 10.4);

Other

5.17 resources required to conduct the study, including time, personnel and equipment, with cost information as appropriate;

5.18 bibliographic references, including citations to unreported data and unpublished studies that may be relied upon in evaluating the results of the study;

5.19 a dated protocol review and approval sign-off sheet;

5.20 addenda, as appropriate, including correspondence, descriptions of any standard operating procedures, representative data collection and consent forms, approval documents, funding documents and agreements with subcontractors; and

5.21 signed, dated amendments to the protocol.

Commentary:

A properly drafted protocol is the linchpin of a well-designed and well-conducted epidemiological study. The protocol should be written to serve as a road map for the study, documenting all major elements of the study design and describing in a reasonably comprehensive manner how the study will be conducted and reported and how study materials will be archived. Requiring the preparation of a reasonably detailed and comprehensive protocol is indispensable for several purposes: (1) to facilitate review of the proposed study on scientific, ethical and data protection grounds and, in particular, to demonstrate that the benefit(s) likely to be derived from the study outweigh any associated risk(s) to the privacy and other rights of research subjects; (2) to confirm compliance with this Code as well as with applicable legal requirements; (3) to enable potential sponsors to make well-informed funding decisions; (4) to enable the principal investigator to manage the study efficiently and control the quality of it; (5) to guide the members of the research team in performing their tasks; (6) to guide quality assurance and verification efforts; and (7) to enhance the reproducibility of the study data and findings. The principal investigator should draft the protocol with those purposes in mind.

The protocol should serve one additional important purpose -- to render the study transparent to persons who did not participate in it so that they can understand it and evaluate the findings, results and conclusions. In order for the protocol to serve that purpose, however, the principal investigator must be prepared to release it to peer reviewers. See Section 8.3.

The protocol should summarize the criteria that will be used to interpret the findings. These should include the steps to be taken in assessing biological plausibility as well as internal and external consistency. The protocol also should identify the criteria that will be used in drawing any causal inferences.

The protocol should be completed prior to the initiation of data collection but may be amended during the course of the study to reflect, among other things, new developments in technology or methodology, other possible improvements in the study design, new information and unforeseen circumstances. The protocol should specify the circumstances under which the approval of the sponsor(s) must be sought for an amendment. In addition, the protocol should specify the procedure (e.g., arbitration) that will be used to resolve disagreements between the sponsor(s) and the principal investigator concerning proposed amendments.

Any significant changes in the protocol, particularly any changes affecting the safety, privacy or well-being of research subjects, may require independent scientific and/or ethical review and approval and/or examination by the relevant data protection authority before implementation. Any significant changes should be documented and appended to the original protocol.

Exploratory analyses raise issues that merit special attention. Typically, an exploratory analysis is designed to assist in formulating a research hypothesis for a future epidemiological study rather than to test such a hypothesis. That means, however, that the process of exploratory analysis is not as rigorous as the process of testing a clearly stated research hypothesis. As a consequence, the results of an exploratory analysis must be interpreted and reported with particular caution. Accordingly, the protocol of every proposed exploratory analysis should disclose clearly that the study is exploratory and that its results will be interpreted and disseminated in a manner that is consistent with the limitations of exploratory research methods.

6.0 Study Conduct

An epidemiological study should be conducted in accordance with the operative protocol. All deviations from the protocol should be documented in writing and authorized by the principal investigator. The documentation should include a statement of the reasons for the deviation and an assessment of the deviation's implications, including any implications relating to study quality and/or obligations to the study sponsor(s) or others.

6.1 Risk of direct harm and discomfort

Whenever the conduct of a study would pose a risk of direct harm or discomfort to research subjects, the appropriate members of the research team should inform prospective participants of the study objective(s) and of the nature of the risk(s) they may incur as a result of their participation. Research subjects should not be deemed to have given their informed consent to participate in a project that might cause them direct harm or discomfort unless they have been informed both orally and in writing of the study's objective(s) and of any associated risk(s) and they have confirmed in writing their complete understanding and acquiescence.

6.2 Data collection and verification

Data collection and verification should be conducted in accordance with the protocol. All data collected in the course of an epidemiological study should be recorded accurately, promptly and in a manner that discloses the identity of the member(s) of the research team having the most complete knowledge of the circumstances under which the data were collected. Any amendment(s) to data entries should be recorded along with the reason(s) for the amendment(s) in a manner that discloses the identity of the member(s) of the research team having the most complete knowledge of the circumstances under which amendment(s) were made. All data should be maintained in a manner that will permit verification. At least one back-up copy of all data should be created and all reasonable steps should be taken to prevent corruption of data.

6.3 Analysis

Data analysis ordinarily should be conducted in accordance with the protocol. Deviations from the statistical methodology described in the protocol should be disclosed whenever reports concerning the study are disseminated. All analyses undertaken in connection with a study should be documented and archived, including in particular analyses that are not disseminated in reports to third parties. All computer programs written in connection with a study and all software packages used, along with their version numbers, should be documented and archived.

6.4 Premature termination

The decision to terminate a study prematurely should be made only in accordance with the protocol. If a decision is made to terminate a study prematurely, the

reasons for that decision should be described in writing, dated and signed by the responsible party (*i.e.*, the person who made the decision to terminate the study). Premature termination of a research project does not relieve members of the research team of their obligations under the applicable data protection legislation or under this *Code*, in particular under Sections 7.0, 8.0 and 10.0.

Commentary:

Compliance with the protocol and documentation of deviations from it should render the research process transparent to those who might wish to reproduce or evaluate the study findings, results and conclusions. Any unexplained failure to comply with the protocol may be tantamount to a breach of faith with the sponsor(s), the persons who conduct the independent scientific and ethical reviews, the quality assurance auditor, the relevant data protection authority, the epidemiological community and the general public. In most cases, amending the protocol is the appropriate way to avoid difficulties that may be created by deviating from the protocol and documenting deviations. See Section 5.13.

While conducting an epidemiological study, the research team should make every effort to protect the integrity of the data. Documentation of data and amendments to data should form an audit trail that the quality assurance auditor can follow when reviewing the conduct of the study. See Section 9.2. Third parties can be sure that a study was conducted in accordance with the protocol and that data were properly collected only if the quality assurance auditor can attest to the integrity of the data.

The issue of premature termination warrants special attention. The protocol should set forth objective circumstances under which a study will or may be terminated. A study might appropriately be terminated, for example, if the response rate is found to be below some defined minimum value on the ground that those persons actually participating in the study do not represent adequately the population of interest. Alternatively, a study might be terminated because obtaining an adequate number of cases within a reasonable period of time has proven to be impossible. Under no circumstances should an epidemiological study be terminated prematurely on the ground that the investigator(s), the sponsor(s) or others are unhappy with study findings or results. The research team's obligations with respect to the dissemination of reports on studies are set forth in Section 8.0 and the accompanying commentary.

7.0 Protecting Personal Data

Personal data should not be collected from or about research subjects unless (1) the data are collected, used and maintained in accordance with the procedures described below and (2) the collection, use and maintenance of the data complies with applicable data protection legislation.

7.1 Informed consent

7.1.1 Whenever data are obtained from the subject

Whenever data or samples are obtained directly from the data subjects, a full written explanation should be provided to the subjects, including details concerning the identity of the principal investigator, the person collecting the data and the purposes for which the data will be used. When researchers meet or telephone subjects, the explanation also should be given orally. When there is no personal interaction with subjects, the questionnaire should include instructions on how further information can be obtained. When written information is the only type provided, a random sample of subjects should be contacted to confirm their understanding of the written explanation. Although the provision of information or samples by a subject may imply consent, a form confirming the receipt and comprehension of information and giving consent should be obtained from the subject.

7.1.2 Whenever data are not obtained from the subject

Whenever data are not obtained directly from the data subjects, it may nevertheless be practicable to obtain their consent to obtain and process their data. If this can be done, information should be provided as described in Section 7.1.1 and a form confirming the receipt and comprehension of information and giving consent should be obtained from the subject.

7.2 Anonymisation

Any personal data that are collected in the course of an epidemiological study should be anonymised as soon as that can be done without compromising the study or as soon as required by the relevant data protection authority, whichever occurs earlier.

7.3 Subject rights

To the extent required by the applicable data protection legislation or the relevant data protection authority, the principal investigator should be prepared to ensure that in response to an appropriate request a member of the research team will do the following without undue delay:

7.3.1 Provide appropriate information to persons who have reason to believe that their personal data are being processed;

7.3.2 Rectify, annotate, erase or block any personal data that are incomplete or inaccurate; and

7.3.3 Notify third parties to whom personal data have been disclosed of any rectification, annotation, erasure or blocking.

7.4 Exemptions if compliance is not practicable

7.4.1 When an exemption mechanism exists

If it is not practicable to comply with the requirements of Sections 7.1 through 7.3, it may be possible to obtain an official exemption. In some cases, the person(s) undertaking the ethical review may be empowered to grant such an exemption. In other cases, the national data protection authority may grant an exemption following the recommendation of those undertaking the ethical review. Whenever it is possible to obtain an exemption, and such an exemption is applied for and granted, the study may proceed. The denial of a request for an exemption means that the study cannot proceed without complying fully with Sections 7.1 through 7.3.

7.4.2 When no exemption mechanism exists

If it is not practicable to comply with the requirements of Sections 7.1 through 7.3 and there is no mechanism for obtaining an exemption, national legislation nevertheless may identify circumstances in which data may be processed without complying with those Sections. If that is the case, the protocol should include a detailed comparison of the actual circumstances with those in which data processing is permitted by national legislation and the persons undertaking the ethical review should rule on whether the actual circumstances justify permitting data processing to proceed. If those undertaking the ethical review agree that the actual circumstances meet the statutory criteria, then the study may proceed. In all other cases, the study cannot proceed without complying fully with Sections 7.1 through 7.3.

7.5 Security prior to anonymisation

Prior to the anonymisation of personal data, the principal investigator should make sure that procedures are in place and are being followed that limit data access to those persons having a demonstrable need for access because of their responsibilities. Unless other procedures are required by the relevant data protection authority, the following procedures should be implemented:

7.5.1 All forms of personal data, whether reduced to writing, maintained electronically or stored in the form of charts, graphs or other depictions, should be kept in a room or other storage facility that is locked when not in use, in which data will be protected from degradation and to which access is controlled by the principal investigator or someone operating under his/her direct supervision;

7.5.2 Passwords should be adopted or other appropriate measures should be implemented to ensure that any copies of personal data being stored in or on a computer, a network or a computer disc cannot be accessed without authorization by the principal investigator;

7.5.3 A list should be maintained, and should be updated to reflect any change of circumstances, of all persons entitled to have access to personal data collected in the course of a study; and

7.5.4 Each person having access to personal data should be required to sign a statement affirming that (1) the person understands the limited purpose(s) for which access has been given; (2) will not disclose personal data to any member of the research team not entitled to access or to any third party; (3) will not take any other action that might undermine the right to privacy or other rights and freedoms possessed by any research subject; and (4) understands that any violation of the applicable data protection legislation may result in the imposition of civil and/or criminal sanctions.

7.6 Studies involving multiple contacts

When the design of a study requires members of the research team to make multiple contacts with the same research subject(s) over a period of time, procedures should be developed to avoid any unnecessary proliferation in the number of people taking responsibility for the recontacts and thus being in possession of personal data with respect to any individual research subject with whom multiple contacts are being made.

7.7 Disseminating findings, results and/or conclusions

Before disseminating the findings, results and/or conclusions of any epidemiological study, special care should be taken to ensure that personal data are not thereby disclosed unless the person to whom the data relate has given informed consent to the disclosure or such disclosure is permitted by the relevant data protection authority.

7.8 Transferring data to third countries

The principal investigator should comply with any restrictions imposed by the applicable data protection law or the relevant data protection authority on the transfer of personal data to third countries. Whenever the applicable data protection legislation or the relevant data protection authority does not permit unrestricted transfer of personal data to a particular country, before transferring data to that country the principal investigator should be prepared to show that adequate safeguards are available to protect the privacy rights of persons whose data are to be transferred and any approvals required for the transfer should be obtained.

7.9 Documenting data security problems

In the event it becomes know that there has been a deviation from any of the security measures described above or required to be implemented by the relevant data protection authority, that fact should be brought promptly to the attention of the principal investigator. The principal investigator should examine the circumstances immediately. If the examination leads the principal investigator to believe that a deviation from required security may have occurred, without delay he/she should (1) notify the relevant data protection authority that a deviation from required security is believed to have occurred with respect to personal data; (2) disclose to the relevant authority what is known concerning the circumstances of the deviation; (3) describe the steps that have been or will be taken to limit any damage to research subjects or others that might be caused by the deviation; and (4) describe the steps the principal investigator proposes to take or has taken to prevent a recurrence. All documents related to a deviation from required security that is notified to any data protection authority should be attached to the study protocol as an addendum.

7.10 Data protection official

The principal investigator should consider appointing a data protection official to ensure that data processing is carried out in a manner that is not likely to affect the rights and freedoms of subjects. The data protection official, if any, should be identified in the protocol. In addition to any duties that may be imposed by the applicable data protection legislation, the data protection official should observe and provide advice on the conduct of all planned and systematic activities implemented to provide adequate confidence that the level of data protection required by this *Code* and/or by the applicable data protection legislation is achieved. The data protection official is not a member of the research team and should be in a position to exercise his or her functions in complete independence.

7.11 Destruction of study materials

All study materials that may contain personal data and that are not to be stored in the study archive should be destroyed in a secure manner at the completion of the study.

Commentary:

Section 7.2 of this Code provides that personal data collected in the course of a study must be anonymised as soon as that can be done without compromising the study. Moreover, under the European Data Protection Directive data will be deemed anonymous only if it is not possible to identify the person to whom the data relate. In practice, however, it may be extremely difficult to render data completely anonymous. For example, even when the data in a particular data base appear to be anonymous because all information linking the data to particular individuals has been destroyed, a person possessing additional data and readily obtainable processing software nevertheless might be able to identify the particular data subjects. Consequently, it is recommended that whenever possible the principal investigator make use of the Section 7.4 exemption

provisions to specify the extent to which data will be rendered anonymous and, whenever appropriate, the reason(s) that complete anonymisation is not possible. In general, the principal investigator should seek to ensure that within a reasonable period of time all data are anonymised sufficiently to ensure that data subjects cannot be identified without a substantial commitment of effort and resources.

One further issue that deserves special attention is the treatment of mortality data and other personal data concerning dead subjects. The provisions of the European Data Protection Directive could be implemented in Member States so as to apply to such data and could require that those data be treated in the same manner as personal data concerning living subjects. National legislation in other cases may exempt personal data related to dead subjects from coverage. This Code takes a flexible approach to the treatment of such data. Whenever a study is covered by Section 7.4, the principal investigator probably will be permitted to adopt reasonable measures for the treatment of such data, subject to the approval of the appropriate authorities. Otherwise, the guidelines are somewhat more demanding but they still should permit epidemiological studies to go forward except in the unlikely event that national legislation itself would prevent research involving the personal data of dead subjects.

The Code encourages the principal investigator to appoint a data protection official to take responsibility for ensuring compliance with all applicable data protection requirements. Appointment of a data protection official may be particularly advisable in countries that provide statutory exemptions from certain data protection requirements for data processed under the supervision of such an official. Under other circumstances, the data protection official may perform a function similar to that of the quality assurance auditor by reviewing and advising on methods for achieving the required level of data protection.

8.0 Disseminating Reports Concerning Epidemiological Studies

The protocol should contain a plan for disseminating study reports. *See* Section 5.12.16. Whenever possible the principal investigator and other members of the research team should follow that plan. Any deviations from the plan should favour broader rather than narrower dissemination within the scientific community.

Whenever a report of a study contains an interpretation of the results, the report should explain the strengths and weaknesses of the interpretation. In particular, the report should disclose the nature and magnitude of any uncertainties as well as the possibilities of error stemming from the manner in which the study was designed and conducted, including the range of possible error related to biases and confounders. Whenever possible, the person(s) disseminating reports also should present competing interpretations of the study results and explain their individual and relative strengths and weaknesses.

A report of the findings, results or conclusions of an epidemiological study should include sufficient information to permit others to make an informed judgment concerning the quality of the data as well as the meaning and implications of the findings, results or conclusions being reported. Whenever possible, reports should be disseminated only after peer review. Whether or not peer review has occurred, however, the person(s) responsible for disseminating a report should ensure full disclosure of any facts or circumstances that are relevant to an evaluation of it.

8.1 Reports

Whenever possible and assuming that the protocol has been made available during peer review in compliance with Section 8.3, reports concerning an epidemiological study typically should include the following information, unless such information can be found in another readily available report:

8.1.1 a descriptive title;

8.1.2 an abstract;

8.1.3 a statement of the extent to which the study complies with this *Code*;

8.1.4 the identity of the sponsor(s) and the author(s) and a statement of any potential conflicts of interest;

8.1.5 a statement of the objectives of the study, including any research hypothesis;

8.1.6 information about initiation and completion dates to the extent relevant;

8.1.7 a description of, or reference to, relevant aspects of the study design (*e.g.*, study type, sample selection procedures, sample size, data collected and methods of data collection), data processing and statistical methodology;

8.1.8 a discussion of the study results and their implications;

8.1.9 a discussion of the findings of statistical analyses that provide an important context for the results included in the particular report;

8.1.10 a discussion of potential sources of error or bias and the extent to which they were controlled, including the outcome of any sensitivity analyses describing the possible individual and collective impact of all potential sources of error or bias;

8.1.11 a discussion of the internal consistency of the study results;

8.1.12 a discussion of the external consistency of the study results;

8.1.13 a discussion of possible biological mechanisms that might explain the results;

8.1.14 a discussion of any elements of the protocol that might affect the interpretation of the results;

8.1.15 a discussion of other factors that should be borne in mind in assessing the meaning of the results;

8.1.16 a discussion of the conclusion(s);

8.1.17 a discussion of any recommendations that the authors might wish to make concerning the appropriate response to their scientific conclusions;

8.1.18 a statement indicating who is responsible for maintaining the study archive and the circumstances under which study materials may be made available for inspection or analysis; and

8.1.19 references.

8.2 Informing study subjects

Whenever reasonably practicable, and particularly when data were obtained from the subjects themselves, all research subjects for a particular study should be informed of the study results and any related interpretation(s). Study subjects should be informed in person, through meetings, video tapes, letters, newsletters, summary reports or other appropriate communication. Study results should be provided in language appropriate for the audience.

8.3 Third party access

It is the responsibility of the principal investigator to ensure that study results are properly disseminated. Under most circumstances, dissemination of study reports, including a comprehensive final report if any, after peer review will be adequate. The protocol should be made available during peer review and relevant details from the protocol should be presented in all study reports. There also are conditions, however, under which third party access to the study materials should be permitted, including (1) updating a study; (2) combining the study data with data from other studies for a pooled analysis or meta-analysis; (3) analyzing data not previously analyzed and reported as part of a project; and (4) re-analyzing and interpreting all or part of a previously analyzed and reported study.

Collaborative efforts in such sharing of study materials are encouraged. Adherence to this *Code*, particularly in preparing the protocol and study reports (*see* Sections 5.0 and 8.0), should facilitate such collaborative efforts. Any time study materials are made available to a third party for further analysis, however, it should be in a manner that is consistent with the proprietary professional interests of the members of the research team, the privacy rights of research subjects and other provisions of this *Code*. *See* Sections 10.3 and 10.4.

Commentary:

Interpreting the results of epidemiological studies is a complex intellectual process requiring scientific judgment that is dependent upon relevant education and practical experience as refined by exposure to peer review. In many cases, an epidemiological study will yield results that are subject to multiple interpretations. It is incumbent upon the epidemiologist to explain and defend the process by which he/she moved from the research hypothesis to the study results and his/her preferred interpretation of those results. Study results can be evaluated and can take their proper place in the scientific literature only if the evidence and reasoning supporting those results are provided in an intelligible form.

In order for others to evaluate the results and interpretation of an epidemiological study, a knowledge of the protocol generally is needed. Ordinarily the recipients of a report on a study will not have reviewed the operative protocol. Therefore, the research team disseminating the report as well as the peer reviewers should ensure that any elements of the protocol that might affect the interpretation of the study results are discussed in the report. If as a result of performing analyses that were not planned in the protocol, a researcher has identified statistical relationships in the data that are not relevant to the original research hypotheses, that fact should be made clear in the report. Special attention should be paid to situations in which research procedures might have introduced or failed to prevent sources of error or bias.

Reports made to the sponsor(s) of an epidemiological study raise unique issues because the sponsor(s) can be expected to have reviewed and approved the protocol and because the sponsor(s) may have imposed specific reporting requirements or conditions on the principal investigator as a condition of providing support for the study.

Reports made to the sponsor(s) should comply with the terms of the protocol as well as with any additional conditions laid down in the sponsorship agreement. Moreover, it is entirely appropriate for the sponsor(s) to request the right to review and comment on study reports before the reports are disseminated. Under no circumstances, however, should the principal investigator permit the sponsor(s) to control the interpretation or impede the timely dissemination of reports on the study.

There is a clear public interest in the widespread dissemination of reports concerning epidemiological studies, at least within the scientific and public health communities. A decision not to disseminate research results can be justified in only the most extraordinary circumstances -- for example, when methodological problems are believed to have deprived the results of any meaning. It should be understood that failure to reject the null hypothesis can be as important as "affirmative" results. Consequently, a decision not to disseminate research results seldom if ever can be justified by the mere failure to find statistically significant associations.

A decision not to disseminate research results, including "negative" or "no-association" findings, contributes to the widely acknowledged problem of publication bias and can distort the conclusions reached in any meta-analyses that may be conducted. Indeed, it is extremely difficult to justify the collection of personal data and the resulting risk to personal privacy unless the study results are placed on the public record so that they can be taken into account by others, including by policy makers.

Some epidemiological studies, such as post-marketing surveillance studies in the pharmaceutical industry, are performed in important part in order to satisfy reporting requirements imposed by regulatory authorities. The obligation to disseminate study results will be satisfied by the filing of a complete report on such a study with a government agency that has imposed specific and detailed reporting requirements. Whenever information contained in such a report is not publicly available, members of the research team should consider disseminating that information to the scientific community after appropriate peer review.

Special care should be taken to avoid over-interpreting or exaggerating the meaning of study results. No public or private interest is served by a research report that fails to disclose relevant information or by a report prepared or presented in a way that causes unnecessary or unwarranted confusion or alarm among policy makers or members of the general public. Compliance with Section 8.0 of this Code should reduce such problems. Of course, a report may include statements about possible public policy implications of the results of a study. But care should be taken to ensure that recipients of the report can distinguish statements that reflect scientific judgments from those that reflect opinions concerning public policy.

Reports should be disseminated in accordance with the plan described in the study protocol. See Section 5.12.16. On occasion, it may be appropriate to disseminate a report on a study in a manner not contemplated by the protocol. Whenever that is the case, the deviation from the protocol should be disclosed and its implications should be explained in the report. In particular, whenever the results of a study are disseminated

prior to the completion of data collection or analysis, that fact should be disclosed and explained.

Agreements between researchers and sponsors or host institutions often require the preparation of a comprehensive final report at the conclusion of an epidemiological study. Researchers should of course comply fully with their contractual and institutional obligations. While the preparation of a comprehensive final report is to be encouraged whenever circumstances permit, institutional or other constraints often may prevent the principal investigator and members of the research team from allocating the time and resources that may be needed to prepare a comprehensive final report when one is not required. In most instances the purposes of a comprehensive final report will be served if results are properly disseminated after peer review. Whenever a comprehensive final report is prepared, it should contain all of the information listed in Section 8.1.

9.0 Quality Assurance

The quality of an epidemiological study depends upon the quality of all facets of the research process, from protocol development to the handling of data, the use of analytic procedures, the interpretation and dissemination of study reports and the archiving of study materials. In the effort to maintain the highest standard of scientific quality, in no area of an epidemiological study should quality assurance be neglected.

9.1 Standard operating procedures

Whenever a task that is critical to a study's quality is to be undertaken repeatedly in the course of the study, standard operating procedures should be used to control the task and thereby ensure that it is conducted in a uniform manner. Particular effort should be made to adopt and follow standard operating procedures whenever tasks are carried out by more than one person and/or over a long period of time. Whenever possible, standard operating procedures should be used that have been validated in other studies under similar circumstances. All standard operating procedures should be described or identified in the protocol. *See* Section 5.12.11.

Whenever the principal investigator determines that it is necessary to modify a standard operating procedure during the course of a study, the modification and the reasons for it should be described in an amendment to the protocol. Whenever the principal investigator determines that it is necessary to modify a process controlled by a standard operating procedure during the course of a study, the modified process and an appropriately modified standard operating procedure should be described in an amendment to the protocol along with an assessment of the likely impact of the modifications on the study. Whenever a process controlled by a standard operating procedure is modified, the modification should be made retroactive, if possible, to those situations in which the unmodified process was used.

9.2 Quality assurance auditor

For each epidemiological study involving the collection and analysis of data, the principal investigator should appoint an individual who is not a member of the research team or employed by the sponsor to serve as the quality assurance auditor. Persons who serve as auditors should have a general familiarity with epidemiological research and extensive experience in data management and analysis. A quality assurance auditor should perform two important functions designed to improve the study's validity. First, the auditor should review, not less frequently than once per year, the research team's compliance with the protocol as well as with any standard operating procedures that have been described or identified in the protocol. Second, the auditor should select for detailed evaluation a random sample of data from those collected and stored by the research team. Aggregate data, including those in tabular form, also should be reviewed. Data should be inspected to determine whether they appear to be correct. Whenever possible, the primary data collection tools (*e.g.*, questionnaire, medical record) should be compared to the data in the electronic file to estimate the study's error rate. If the auditor detects evidence of

fraud or other scientific misconduct, that fact should be reported immediately to the primary investigator and the sponsor(s) both orally and in writing.

9.3 Periodic audit reports

After each periodic review, the quality assurance auditor should present the results of the review in writing to the principal investigator and to the sponsor(s). The principal investigator should respond in writing to the report and should describe any steps taken or contemplated in response to any serious problems that were identified. The auditor's periodic reports and the principal investigator's responses should be maintained in the study archive.

9.4 Final quality assurance report

The quality assurance auditor should prepare and sign a final report attesting to the extent of compliance of the study with the protocol and standard operating procedures. This report should describe any quality assurance or performance problems that were identified during the course of the study. The report also should review the responses provided by the principal investigator to the quality assurance auditor's periodic reports and indicate whether those responses were adequate. The final quality assurance report should be presented to the study sponsor(s) and maintained in the archive.

9.5 Transmittal to data protection authority

Whenever required by the applicable data protection legislation or the relevant data protection authority, a copy of all audit reports and of responses thereto should be forwarded promptly to the relevant data protection authority. The reports and responses should permit the data protection authority to determine whether any departures from the study protocol are likely to affect in an adverse manner the privacy rights and interests of research subjects and whether the study otherwise is being conducted in accordance with any instructions that were given.

Commentary:

The public, the scientific community, research teams and study sponsors all have a strong interest in ensuring the quality of epidemiological studies. The primary responsibility for controlling and ensuring the quality of a study rests, of course, with the study's principal investigator. See Section 4.4. In order to increase the confidence of third parties, however, this Code incorporates two requirements that are designed to provide independent assurance of some important aspects of study quality.

First, just as the protocol should both guide and document the conduct of the study as a whole, so standard operating procedures (SOPs) should guide and document individual activities that have to be undertaken repeatedly and consistently in the course of the study. SOPs are particularly important whenever an activity is repeated by different people and/or over a long period of time under circumstances in which, even with initial training, the conduct of the activity may change, thereby leading to a loss of consistency. SOPs may cover many aspects of a study, such as techniques for analyzing

data, the structure of an interview and the maintenance of the chain of custody for samples gathered in the course of the study.

For some repetitive activities, e.g., the reading of radiographs for diffuse changes or the conduct of lung-function tests, there are well-established descriptions of validated SOPs. In other instances, the research team may be able to use SOPs that have been validated in previous studies that the team has conducted. Whenever there is no validated SOP available and an SOP would be useful, the principal investigator should consider developing an appropriate SOP and validating it in a pilot study (or a pilot phase of the actual study) that simulates to the extent possible the circumstances of the actual study.

The principle investigator should consider making changes in an SOP whenever (1) the SOP is unambiguous but the process controlled by the SOP requires modification or (2) the SOP is ambiguous and, as a result, there are variations or inconsistencies in the process that it controls. Any changes made to an SOP should be described in a protocol amendment along with the date of the change, the reasons for it and an assessment of its likely impact. Consideration should be given to making modifications retroactive if this would improve consistency without introducing bias.

Second, every epidemiological study should be monitored by an independent quality assurance auditor responsible for ensuring that the study complies with the protocol and with any standard operating procedures identified in the protocol or developed for use in the study. The presence of an independent expert auditing compliance with the protocol and standard operating procedures should encourage members of the research team to maintain the quality of the research activity. The auditor's written final report also will increase confidence in the quality of the study by providing the sponsor(s) with the opportunity to review an objective discussion of any quality assurance or performance problems that may have arisen during the course of the study.

On occasion the auditor's final report may contain personal data that are covered by applicable data protection legislation. In those circumstances, the auditor should be prepared to produce an expurgated version of the final report.

In recent years there have been a number of well-publicized reports of misconduct by investigators in various scientific disciplines, including epidemiology. A properly designed and conducted quality assurance program should detect many forms of misconduct. Consequently, one important effect of a quality assurance program should be to give assurance to third parties that reports about the research and its results are trustworthy. It must be recognized, however, that no quality assurance program can provide an absolute guarantee against misconduct.

10.0 Archiving Study Materials

Every epidemiological study should have an archive associated with it. The sponsorship agreement should indicate clearly which party owns the study materials and bears responsibility for managing the archive. *See* Section 4.1. Regardless of which party maintains and manages the archive, however, the principal investigator bears responsibility for creating the archive by selecting and preparing study materials for storage. *See* Section 4.4.

10.1 Contents of the archive

A physically secure archive for the orderly storage and expedient retrieval of study materials should be provided and maintained in accordance with the protocol and the sponsorship agreement. An index should be prepared to identify archived materials and to facilitate their retrieval. At a minimum, the archive should contain the study materials set forth below. Additional materials may have to be maintained in the archive under applicable legislation or the sponsorship agreement.

10.1.1 the study protocol, with any appendices required by this *Code*, and copies of all modifications with appropriate approvals;

10.1.2 a copy of the comprehensive final report, if one is prepared, as well as copies of all published articles, documentation describing any other presentation relating to the study and any relevant peer review reports;

10.1.3 to the extent permitted by applicable data protection legislation, all source data and interviewer notes and, if feasible, other samples and specimens;

10.1.4 the master computer data file and sufficient coding and other information to permit the study data to be processed in accordance with the provisions of this *Code*;

10.1.5 documentation adequate to identify and locate all computer programs, including version numbers where appropriate;

10.1.6 documentation for any manually developed calculations;

10.1.7 periodic and final reports from the independent quality assurance auditor; and

10.1.8 correspondence and other documents relating to the study, including those bearing upon the privacy rights addressed in the applicable data protection legislation.

10.2 Maintenance of the archive

The study archive should be maintained in accordance with the protocol for a period of at least ten years from the completion of the study unless the applicable legislation, the relevant data protection authority or the sponsorship agreement recommends or requires a different period.

10.3 Access to the archive

Access to the archive should be limited to authorized persons. Each person who receives access to personal data within the archive should be required to sign a statement affirming that the person (1) understands the limited purpose(s) for which access has been given; (2) will not disclose personal data to anyone; (3) will not take any other action that might undermine the right to privacy or other rights and freedoms possessed by any research subject; and (4) understands that any violation of the applicable data protection legislation may result in the imposition of civil and/or criminal sanctions. This signed statement should be maintained in the archive with other materials related to data protection.

10.4 Analysis and processing of study materials

Each person who receives access to study materials stored in the archive and who proposes to analyze or process those materials in any manner should be required to sign a statement affirming that the person will abide fully by the terms of this *Code*. In addition, before being given access to personal data stored in the archive, the person should present evidence showing that the proposed processing has been authorized by the relevant data protection authority or otherwise is permissible under the applicable data protection legislation.

Commentary

The archive is a critical component of an epidemiological study. The archive should be assembled and managed in a manner that preserves study materials for (1) further analysis and interpretation by members of the research team; (2) further quality assurance review whenever necessary; and (3) further analysis by third parties who are authorized to evaluate the research team's reports or to extend the research team's work.

Creating and managing an archive inevitably involves both burden and expense. Consequently, an effort has been made to limit the types of materials that must be maintained in the archive to those that are essential to the purposes identified above. The Code also limits the administrative burdens to those that are associated with the need to comply with applicable data protection requirements.

11.0 References

[Insert reference list]

Huntingdon

Dr. Has Shah
CMA
1300 Wilson Boulevard
Arlington, VA 22209

15 December, 1997

Dear Dr. Has Shah:

Huntingdon concludes its lawsuit against People for the Ethical Treatment of Animals (PETA)

Costly, but essential litigation launched by Huntingdon in July 1997 to get back documents, information, proprietary knowledge and clients' trade secrets taken by PETA has been settled before proceeding to trial.

The settlement is in the form of a court order and PETA has agreed to be legally bound:

1. **NOT** to participate in or encourage or fund others to carry out any undercover or surreptitious information gathering activities at Huntingdon for 5 years.

2. **NOT** to contact or to interfere with Huntingdon, its employees, clients (or study monitors), suppliers or business relationships.

3. **NOT** to urge nor to suggest to any individual or business entity that they should not do business with Huntingdon.

4. **NOT** to disclose or disseminate any of the information, documents, or materials concerning Huntingdon or its clients obtained from Huntingdon or discovered during litigation.

Additionally, PETA must return or destroy all documents, information and materials in whatever form taken or obtained from Huntingdon or obtained during the discovery phase of the litigation.

Under the agreement PETA is able to comment on certain materials already in the public domain but they cannot link such information to Huntingdon or its clients unless the material already does so and they cannot use it in any campaign against Huntingdon or its clients.

PETA has agreed that the 3 'R's (Reduction, Refinement and Replacement) are part of Huntingdon's business objectives. At the same time Huntingdon, without giving any commitment to respond or to accept, will present certain recommendations of PETA to its IACUC.

The settlement of the lawsuit means Huntingdon can focus all its energies on its relationships with its clients many of whom have seen for themselves the continuation of improvements throughout 1997, which Huntingdon commenced at Princeton in 1996.

Yours sincerely,

Alan Staple
President

BFG40876

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Tel: +1 908 873 2550 Fax: +1 908 873 3992

CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

October 15, 1997

Ms. Anne Pope
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Mail Drop 14
Research Triangle Park, NC 27711

Re: Clean Air Act Section 112(k) Urban Air Toxics Program

Dear Ms.Pope:

The Vinyl Chloride Panel of the Chemical Manufacturers Association (CMA) is pleased to submit the attached comments on the information recently made available via the Internet on EPA's Urban Air Toxics Program under Section 112(k) of the Clean Air Act.

The Panel appreciates EPA's consideration of these comments. If you have any questions or would like additional information, please call Ms. Wendy K. Sherman, Manager of the Vinyl Chloride Panel, at (703) 741-5639.

Sincerely yours,

BFG40877

CHEMICAL MANUFACTURERS ASSOCIATION

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

October 15, 1997

Ms. Laura McKelvey
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Mail Drop 15
Research Triangle Park, NC 27711

Re: Clean Air Act Section 112(k) Urban Air Toxics Program

Dear Ms. McKelvey:

The Vinyl Chloride Panel of the Chemical Manufacturers Association (CMA) is pleased to submit the attached comments on the information recently made available via the Internet on EPA's Urban Air Toxics Program under Section 112(k) of the Clean Air Act.

The Panel appreciates EPA's consideration of these comments. If you have any questions or would like additional information, please call Ms. Wendy K. Sherman, Manager of the Vinyl Chloride Panel, at (703) 741-5639.

Sincerely yours,

BFG40878

BFG 00377

Before the
U.S. Environmental Protection Agency

COMMENTS OF THE VINYL CHLORIDE PANEL OF THE CHEMICAL MANUFACTURERS ASSOCIATION ON EPA'S URBAN AIR TOXICS PROGRAM UNDER CLEAN AIR ACT SECTION 112(k)

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October 15, 1997

CHEMICAL MANUFACTURERS ASSOCIATION
1300 Wilson Boulevard
Arlington, Virginia 22209
703/741-5000

EXECUTIVE SUMMARY

The Vinyl Chloride Panel of the Chemical Manufacturers Association (CMA) is pleased to submit these comments on the information recently made available via the Internet on EPA's Urban Air Toxics Program under Section 112(k) of the Clean Air Act. The Panel's comments raise the following points:

- EPA's emissions estimates for vinyl chloride are flawed. Its calculations of the amount of vinyl chloride emitted in 1990 greatly exceed the amounts actually recorded on the Toxic Release Inventory (TRI), by as much as two or three orders of magnitude. EPA fails to explain how it developed the methodology that it used for these calculations, or why it would be preferable to the TRI data when vinyl chloride is emitted almost entirely by chemical manufacturers, who are all required to report to the TRI data base.

- EPA also fails to explain how it assigned emissions to particular source categories. EPA appears to have developed the estimates in the Inventory solely on the basis of assumptions as to what activities result in emissions, and what percentage of those activities come from area or major sources.

- Aside from questions as to their accuracy, EPA's emissions data indicate that vinyl chloride should not be included in the Section 112(k) Inventory. because emissions from area sources are insignificant. Less than 3 percent of the total vinyl chloride emissions in urban areas come from area sources.

- The clear purpose of Section 112(k) is to reduce emissions from area sources, and inclusion of vinyl chloride in the Inventory is not consistent with this mandate. Both the structure and legislative history of Section 112(k) indicate that Congress intended EPA to prepare a strategy for regulating emissions from area sources, which are not subject to regulations addressing residual risk to be issued under Section 112(f) of the Clean Air Act.

- EPA is directed to (i) identify area sources of at least 30 hazardous air pollutants (HAPs) that present the greatest threat to urban populations; (ii) assure that sources that account for 90 percent or more of the aggregate emissions are subject to regulation; and (iii) develop a national strategy to reduce cancer attributable to these pollutants by at least 75 percent. Vinyl chloride, 94 percent of whose emissions come from a single major source category, is already strictly regulated under the maximum achievable control technology (MACT) standards, and does not fit any of the criteria for EPA's strategy. Even the strictest regulation of vinyl chloride emissions from area sources would not affect the health threat to urban populations or reduce cancer risks attributable to exposure to HAPs.

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INTRODUCTION

The Vinyl Chloride Panel[1] of the Chemical Manufacturers Association appreciates the opportunity to provide comments on the external review draft of the 1990 Emissions Inventory of Forty Section 112(k) Pollutants, which is intended to provide supporting data for a future Environmental Protection Agency (EPA) regulatory strategy for improving air quality and public health in urban areas pursuant to Section 112(k) of the Clean Air Act. EPA has stated that the list is a starting point for further analysis under EPA's Urban Air Toxics Study. The Panel believes that vinyl chloride does not meet the criteria for regulation under Section 112(k), and should be removed from the Inventory.

The Panel appreciates the efforts that EPA has undertaken to compile the information contained in the draft Inventory. The inclusion of vinyl chloride as one of the pollutants in the Inventory, however, will not further the goals identified in Section 112(k). EPA articulates a three-step procedure that Section 112(k) imposes relating to the Inventory: (i) identification of area sources of at least 30 hazardous air pollutants (HAPs) that present the greatest threat to urban populations; (ii) assurance that sources that account for 90 percent or more of the aggregate emissions are subject to regulation; and (iii) development of a national strategy to reduce cancer attributable to these pollutants by at least 75 percent. The inclusion of vinyl chloride in the inventory, and in any strategy that might be based on it, will not serve any of these purposes. The focus of Section 112(k) is on area sources, *i.e.*, those that emit fewer than 10 tons per year of any individual HAP and fewer than 25 tons per year of any

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[1] The members of the Vinyl Chloride Panel include PPG Industries, Inc., the GEON Company, Westlake Polymers, Borden, Inc., BF Goodrich, Occidental Chemicals, The Dow Chemical Co., CONDEA Vista Company, Formosa Plastics, and Georgia Gulf Corp.

combination of HAPs.[2] EPA's own data show that vinyl chloride is not present in urban areas as a result of emissions from area sources in any significant amounts. Its inclusion in the Inventory would not be consistent with the statutory mandate. By listing vinyl chloride in the Inventory, along with a number of other chemicals that are not emitted from area sources in any significant quantity, EPA seems to have conflated the provisions of Section 112(k) dealing specifically with area sources and those dealing with stationary sources as a whole. Vinyl chloride should not be included in the Inventory and it certainly should not be the subject of any national strategy focused on reducing emissions of HAPs from area sources in urban areas.

I. EPA SHOULD PROVIDE MORE INFORMATION ON THE SELECTION OF THE 40 HAPS LISTED

EPA selected the 40 HAPs included in the inventory from among the 188 HAPs listed in Section 112(b) of the Act. The public should be informed as to EPA's rationale for selection of these particular 40 substances *before* it is asked to review emissions estimates developed by EPA. No explanation is provided, however, as to how EPA chose the 40 HAPs identified. The introduction (p. 1-1) contains a vague reference to the use of "[a]vailable toxicity, ambient monitoring, and emissions inventory data, and results from existing exposure and risk assessment studies" to develop the list, but identification of these obvious criteria is meaningless without an explanation as to how they were applied by EPA. For the comment process to be productive, EPA should provide a much more detailed explanation of how it selected each HAP that it proposes to include in the Inventory, including how the available

[2] 42 U.S.C. § 7412(b)(1)-(2).

toxicity and emissions data support the conclusion that "as the result of emissions from area sources," it presents "the greatest threat to public health in the largest number of urban areas."[3]

II. EPA'S EMISSIONS ESTIMATES ARE FLAWED

In addition to the legal and policy objections discussed below, from a purely empirical standpoint EPA's emissions data appear to be seriously flawed. EPA did not use the most widely accepted source for such emissions, its own Toxics Release Inventory (TRI), as the basis for its emissions from chemical manufacturing and perhaps other source categories. Instead, it performed a calculation based on production capacity and an "emissions factor." The resulting estimates show emissions of vinyl chloride in 1990 that greatly exceed the actual data shown in the 1990 TRI report, often by two or three orders of magnitude. Thus, for example, EPA calculates that Dow Chemical's Plaquemine, Louisiana plant emitted 3,012.06 tons of vinyl chloride in 1990, while the TRI report indicates that only 3.75 tons were emitted. Similarly, EPA calculates that Occidental Chemical's Deer Park, Texas facility emitted 2548.67 tons of vinyl chloride in 1990, when the TRI report indicates that only 0.0435 tons were emitted. Examination of the figures reveals a similar discrepancy for each manufacturing facility. The 1990 TRI data for vinyl chloride are attached.

EPA has given no clear explanation as to why the TRI data were not considered sufficient for purposes of estimating emissions from the chemical manufacturing process. It also has not provided a sufficient discussion of why the "emissions factor" calculation is considered more appropriate. In the introductory section to the Inventory (pp. 4-3, 4-4), EPA

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[3] 42 U.S.C. § 7412(k)(3)(B)(i).

states that there are limitations to the use of the TRI data, primarily that not all sources are required to report to the TRI data base. Whatever the merits of this reasoning generally, it would not appear to apply to the chemical manufacturers that make up the overwhelming majority of vinyl chloride emitters. For example, EPA states that the TRI data may not be entirely reliable because some facilities might be able to avoid TRI data reporting requirements based on the chemical threshold criteria, *i.e.*, manufacture or processing of more than 12.5 tons per year of a listed chemical or use of more than 5 tons per year of a listed chemical. This concern does not apply in the case of chemical manufacturers responsible for emissions of vinyl chloride, and presumably to chemical manufacturers in general. In light of the large discrepancies between the numbers that EPA calculated and those actually reported on the TRI, the Agency has a significant burden to justify its theoretical attempt to derive values for emissions.

Even more significant for purposes of developing an Inventory of urban air toxics from area sources is the approach EPA apparently used to develop its emissions estimates for other source categories. EPA apparently assigned each company reporting emissions of vinyl chloride on the 1990 TRI to a source category based on assumptions as to the likelihood that it would be engaged in a particular line of business. Then, for each source category, EPA came up with percentages of emissions from that category that would be deemed to be from area sources and percentages that would be deemed to be from major sources. These major/area percentages were then applied to the total national emissions of each pollutant from each source category to calculate the major and area source emissions for that category. EPA does not detail how it chose to allocate emissions into source categories, nor does it explain how it

derived the percentages for area and major sources, either in the aggregate or on the basis of individual categories, except to say that the emissions were spatially allocated. It is hard to tell whether anything more than guesswork was involved. It appears that EPA took one set of assumptions (the assignment of the emissions to source categories) and combined it with another set of assumptions (the percentage of major and area sources for each category) to come up with the estimates in the Inventory.

It is difficult for the Panel to say more about the methodology used absent reverse engineering. One important point must be emphasized, however: EPA's estimates in Table 6-41 do not comport with the Panel's empirical knowledge as to sources of vinyl chloride emissions. Table 6-41 shows a number of source categories for vinyl chloride that purportedly result in area source emissions, including such categories as petroleum refining and agricultural chemicals. To the best of our knowledge, vinyl chloride is not used in these industries. As the Agency for Toxic Substances and Disease Registry (ATSDR) recognized in its Toxicological Profile for vinyl chloride, "[v]inyl chloride is used almost exclusively in the United States by the plastics industry for the production of PVC and several copolymers."[4] The overwhelming majority of vinyl chloride emissions is from major sources which manufacture vinyl chloride and polyvinyl chloride (PVC) and which fall within a single source category -- chemical manufacturing.

The remaining source categories where vinyl chloride emissions are possible are in those industries which extrude PVC to make articles such as PVC pipe, upholstery for automobiles, and vinyl wall coverings. Such categories may emit small amounts of vinyl

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[4] U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Toxicological Profile for Vinyl Chloride, Update, 87 (1993).

chloride during the extrusion process. The limited use of vinyl chloride outside of chemical manufacturing reflects the fact that it is a Group A carcinogen and is stringently regulated by EPA and other regulatory agencies. For example, the Occupational Safety and Health Administration enforces a 1 part-per-million exposure limit for vinyl chloride, 29 CFR § 1910.1017(c), as well as ancillary provisions. These regulations discourage its use except in well-controlled operations.

The largest source category of emissions of vinyl chloride identified by EPA, other than chemical manufacturing, is "Landfills: chemical waste emissions." Miscellaneous treatment, storage and disposal facilities are already listed under Section 112(c) of the Clean Air Act. EPA has implemented regulatory standards that control their emissions of HAPs, including standards of performance for new municipal solid waste landfills and emissions guidelines for existing municipal solid waste landfills. 40 C.F.R. §§ 60.30c, 60.750. These standards regulate the design and operation of such facilities. Such facilities are regulated extensively by EPA under the Resource Conservation and Recovery Act. It is not clear how, as a practical matter, any additional standards issued under Section 112(k) could impose requirements that would result in meaningful additional reductions in emissions given the comprehensive regulatory schemes already in place.

III. THE LANGUAGE AND STRUCTURE OF SECTION 112(k) DO NOT SUPPORT THE INCLUSION OF VINYL CHLORIDE IN THE INITIAL INVENTORY OR IN ANY STRATEGIES THAT ARE BASED ON IT

In preparing the Inventory, EPA appears to have lost sight of the Section 112(k) mandate to identify the HAPs emitted from *area* sources in urban areas. Instead, it seems to

have prepared the Inventory to include any HAPs emitted in urban areas, regardless of their source. Both the language and structure of Section 112(k), however, make clear that it authorizes a regulatory program only for HAPs emitted from area sources.

The specific focus of Section 112(k) is readily apparent from its title -- "Area Source Program." Section 112(k)(1), "Findings and Purpose," makes this even more clear. It begins with the statement that "[t]he Congress finds that emissions of hazardous air pollutants *from area sources* may individually, or in the aggregate, present significant risks to public health in urban areas."[5] It then goes on to state:

> It is the purpose of this subsection to achieve a substantial reduction in emissions of hazardous air pollutants *from area sources* and an equivalent reduction in the public health risks *associated with such sources* including a reduction of not less than 75 per centum in the incidence of cancer attributable to emissions from such sources.[6]

The unmistakable focus is on area sources. Vinyl chloride, which is emitted overwhelmingly from major sources, is not the kind of air pollutant at which this subsection is aimed. Section 112(k)(2) requires EPA to conduct research, in consultation with state and local air pollution control officials, on sources of HAPs in urban areas. This research is to form the basis for the Agency's strategy to reduce emissions. The statute specifically states that the program must include an analysis to characterize the sources of the HAPs, "with a focus on area sources and the contributions that such sources make to public health risks from hazardous air pollutants."[7] The express goal of the research program, of which the Inventory is a partial result, is to identify HAPs that are emitted specifically from *area sources*.

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[5] 42 U.S.C. § 7412(k)(1) (emphasis added).

[6] *Id.* (emphasis added).

[7] 42 U.S.C. § 7412(k)(2)(B).

Once EPA has completed its research program, it is directed by the statute to develop a national strategy to reduce the harmful effects of HAP emissions on public health. EPA has described the Inventory as the first step in the development of this strategy. The national strategy identified in Section 112(k) consists of three parts -- identification of area sources of at least 30 hazardous air pollutants, assurance that sources accounting for 90 percent or more of aggregate emissions are subject to regulation, and development of a national strategy for 75 percent reduction in cancer incidence -- which are the three goals cited by EPA as the basis for formulating the inventory. An examination of the subparagraphs of Section 112(k) that give rise to the specific duties cited by EPA reveals that vinyl chloride is not an appropriate subject for the strategy.

A. Vinyl Chloride Does Not Fit the Criteria For HAPs To Be Included in the Inventory

Section 112(k)(3)(B)(i) provides the first prong for the development of a national strategy. EPA is to "identify not less than 30 hazardous air pollutants which, as the result of emissions from area sources, present the greatest threat to public health in the largest number of urban areas and that are or will be listed pursuant to subsection (b)."[8] Even a brief consideration of this language indicates that vinyl chloride does not fit the criteria for HAPs on the Inventory. The HAPs identified are to be the ones that present the greatest threat to public health as the result of emissions from area sources. Moreover, that threat is not to be one that is confined to an individual locality but must occur in "the largest number of urban areas." As noted above, the total emissions of vinyl chloride from area sources are extremely small. It is

[8] Section 112(b) is, of course, the list of HAPs established by Congress, to be modified by EPA as appropriate.

an unlikely candidate for posing the greatest threat to the public health in the largest number of urban areas.

B. One Major Source Category of Vinyl Chloride Accounts for Over 90 Percent of Aggregate Emissions

After EPA compiles the list of 30 or more HAPs emitted from area sources, it is directed by Section 112(k)(3)(B)(ii) to identify the source categories or subcategories emitting such HAPs "that are or will be listed pursuant to subsection (c)," and to "assure that sources accounting for 90 per centum or more of the aggregate emissions of each of the 30 identified hazardous air pollutants are subject to standards pursuant to subsection (d)." Section 112(d) provides for the establishment and imposition of maximum achievable control technology ("MACT") requirements on major and area sources.

As noted above, the area sources for vinyl chloride account for only a tiny percentage of its total emissions. Using EPA's own data (pp. 6-123, 6-124), the chemical manufacturing source category alone accounts for 94 percent of aggregate vinyl chloride emissions. Even if the estimate should change, it is clear that most of the aggregate emissions of vinyl chloride are already regulated by the MACT standard for synthetic organic chemical manufacturing. Listing of vinyl chloride in the Inventory is thus unnecessary for EPA to assure itself as to this point.

C. Reduction of Area Source Emissions of Vinyl Chloride Will Not Advance the Goal of Reducing Cancer Incidence by 75 Percent

The third prong of the 112(k) strategy directs EPA to prepare a course of regulatory action based upon the above findings. Section 112(k)(3)(C) provides that:

> "[t]he strategy shall include a schedule of specific actions to substantially reduce the public health risks posed by the release of hazardous air pollutants from *area sources* . . . . . The strategy shall achieve a reduction in the incidence of cancer attributable to exposure to hazardous air pollutants emitted by stationary sources of not less than 75 per centum, considering control of emissions of hazardous air pollutants from all stationary sources and resulting from measures implemented by the Administrator or the States under this or other laws.

The regulatory strategy prescribed by Section 112(k) must result in a 75 percent decrease in cancer attributable to exposure to HAPs. It must focus on reducing exposure to the HAPs identified by EPA, but it must do so by identifying regulatory actions aimed at *area sources*, as those are the only sources that EPA is authorized to regulate by Section 112(k)(3). As noted above, emissions of vinyl chloride from area sources comprise only a tiny fraction of a percent of the total HAP emissions from area sources. Even if it were possible to eliminate emissions from these sources, there would be little effect on overall exposure to vinyl chloride because of the overwhelming predominance of major sources. This would not advance the objective of Section 112(k) -- a decrease in cancer attributable to all stationary sources of HAPs.

D. The Structure and History of Section 112

The narrow purpose of Section 112(k) is apparent from the overall structure and legislative history of Section 112. Section 112(f)(1)(A) provides that EPA shall develop and report to Congress on methods of calculating the risk to public health remaining from sources subject to MACT regulation, the so-called "residual risk" determination. Section 112(f)(5) provides that EPA will not be required to conduct any residual risk determination or promulgate emissions limitations "for any category or subcategory of area sources that is listed

pursuant to subsection (c)(3) and for which an emission standard is promulgated pursuant to subsection (d)(5)." This exception recognizes the fact that area sources are different from major sources and should be regulated under a unique standard of their own, *i.e.*, that established by section 112(d)(5) and 112(k). The sponsors of the amendment that became Section 112(f)(5) stated that area sources have very different emission patterns from major sources, and that they are often small businesses, which do not have the resources to conduct alternative demographic risk analyses or achieve the emissions levels that might be required by standards issued under the residual risk provisions of Section 112(f). "[T]o impose on each individual area source the same degree of regulation that you would impose on a major toxic air source is unmerited."[9]

Section 112(f)(5) was added to ensure that a distinct regulatory program would apply to area sources. In commenting on the amendment, Senator Moynihan indicated that the residual risk provisions were not only inappropriate for area sources, they were unnecessary, as Section 112(k) provided for a different approach.

> Historically, EPA has found it difficult to deal with these area sources. The traditional approach of promulgating emission standards or alternative design and work practice standards were often inappropriate and cumbersome for regulating many of the area sources. In preparing the clean air bill, the Environment and Public Works Committee tried to provide EPA with the tools needed to deal effectively with area source emissions of air toxics. *Specifically, section 112(k) was added.*[10]

The legislative history of Section 112(k) confirms that Congress intended it to grant EPA the authority to regulate emissions not effectively covered by the regulations issued under

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[9] 136 Cong. Rec. S3768 (daily ed. April 3, 1990) (statement of Sen. Symms).

[10] 136 Cong. Rec. S3769 (daily ed. April 3, 1990) (emphasis added).

other subsections of Section 112, such as standards to reduce residual risk under Section 112(f). The Committee Report on the amendments that included what is now Section 112(k) stated that EPA had found through a series of studies conducted throughout the 1980s that "only a part of the air toxics problem results from the large chemical and industrial facilities which one normally associates with hazardous air pollutants. A substantial portion of the air toxics problem may, in fact, be caused by much smaller, diverse sources of these air pollutants." These smaller sources, the area sources, were not effectively regulated by the statutory mechanisms available to EPA at that time.

> In many cases, the authorities of section 112 (promulgation of emissions standards or alternative design and work practices standards) would have been cumbersome tools, at best, to achieve reductions in pollution from these sources. The Agency, therefore, turned to other authorities in the Clean Air Act (new source performance standards and mobile source tailpipe standards) and other statutes (the Toxic Substances Control Act principally) to develop the needed tools . . . The new section 112(k) proposed in this legislation builds on the Agency's plans to address this portion of the air toxics problem.[11]

Thus, the purpose of Section 112(k) is to enable EPA to act against HAPs which are not readily controlled through regulations on major sources, but which are nonetheless emitted in significant amounts, *i.e.*, "the substantial portion of the air toxics problem" identified by EPA and by Congress in the legislative history. This discussion makes clear that Section 112(k) is not intended to authorize additional and unnecessary regulations on area sources that result in only minute exposure to a HAP, especially if the HAP is actually emitted almost entirely through major sources that are already effectively regulated by EPA. Vinyl chloride,

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[11] S. Rep. No. 101-228, 101st Cong. 1st Sess. at 186 (1989).

a substance whose exposure results overwhelmingly from major sources, is not an appropriate HAP for consideration under Section 112(k) of the Clean Air Act.

CONCLUSION

The inclusion of vinyl chloride in EPA's 1990 Emissions Inventory of Forty Section 112(k) Pollutants does nothing to achieve the goals set by Section 112(k) of the Clean Air Act. The emissions of vinyl chloride from area sources in urban areas are minimal and insignificant when compared with the emissions of other HAPs on the Inventory. Vinyl chloride should be eliminated from the Section 112(k) Inventory.

Attachment