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ETHICAL ISSUES IN OCCUPATIONAL HEALTH RESEARCH

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The purpose of this article is to highlight important issues in the design, conduct, and review of human-subjects research studies in occupational health. The article will do this within the framework of ethical guidelines and regulations governing human-subjects research in the U.S., and will draw from the authors' experience as researchers and members of the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH).

In the U.S., research that is supported or regulated by any of 17 Federal Agencies is subject to oversight requirements that are described in "the Common Rule," also known as 45 CFR 46.[10] These requirements include review of research protocols by local institutional review boards (IRBs), whose members include both scientists and non-scientists (e.g., lawyers, ethicists, and clergy) and persons who are not affiliated with the institution. IRBs review research protocols to assure that risks to human subjects are minimized and informed consent is obtained.[10] Many organizations not covered by Federal human-subjects regulations have established review procedures similar to those required by the regulations. A non-profit organization, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) is in the process of developing an accreditation system for human research protection programs.[2]

The basic ethical principles involved in research with human subjects are described in the Belmont Report, which was developed by the National Commission for the Protection of Human

Subjects of Biomedical and Behavioral Research.[3] The Belmont Report describes three ethical principles which serve as a justification for many particular ethical prescriptions and evaluations of human actions. These are the principles of respect for persons, beneficence, and justice. The concept of **respect for persons** incorporates both the requirement to acknowledge autonomy and to protect those with diminished autonomy. Respect for persons demands that subjects enter into research voluntarily and with adequate information. Circumstances in which the researcher must be concerned about the individual's capacity for self-determination include illness, mental disability, and severe restriction of liberty.

The term **beneficence,** as used in the Belmont report, is the obligation of the researcher to "do not harm; and maximize potential benefits, and minimize potential harms." The principle of beneficence applies both to individual research projects and to the entire enterprise of research. In the case of specific projects, investigators and their institutions are obligated to plan projects in such a way that benefits are maximized and risks minimized.

The concept of **justice** requires the investigator to consider the question: "Who ought to receive the benefits of research and bear its burdens?" The selection of research subjects must be evaluated to determine whether some classes are being systematically selected because of their easy availability or manipulation, rather than for reasons directly related to the problems being studied. Demographic groups should not be asked to disproportionately bear the risks of research that will benefit others. Similarly, research designs should not arbitrarily exclude groups of individuals from studies that might benefit them.

Federal regulations for human-subjects research prescribe special rules for research involving vulnerable populations, such as pregnant women, children, and prisoners. Rothstein has argued that workers should be considered vulnerable subjects of research and afforded additional protections beyond those normally provided research participants.[16] He has proposed guidelines for research involving workers to ensure that consent for participation is truly voluntary and that risks are minimized and benefits maximized. These guidelines include:

1. If possible, the research should be performed by a party other than the employer in order to avoid coercion or perceived conflicts of interest.*
2. Employers and employees (including union representatives) should be involved from the beginning in developing all aspects of the study.
3. The sponsor of the research must be indicated to potential participants, and investigators must disclose any financial interests in the research.
4. Individuals with supervisory authority over potential research participants should not be involved in the recruitment process, and lists of participants should not be shared with supervisors.
5. No inducements that might affect the worker's ability to make an informed, voluntary choice about participation should be offered.
6. The informed consent process should make clear that there will be no adverse employment consequences for declining to participate or withdrawing from the research; potential participants should also be informed whether treatment or compensation for injuries will be provided.
7. Research should be conducted, and results should be disclosed, in the least identifiable form consistent with sound scientific methodology.
8. If the investigators believe that the findings will be of sufficient scientific va-

*A number of companies conduct record-based epidemiologic surveillance and research studies, and it has been argued that these can be designed so that they are consistent with ethical principles.[6]

lidity and clinical utility to warrant offering participants the opportunity to obtain their individual results, the participants should be advised of all potential risks of disclosure, including any psychological, social, or economic risks.

9. Reasonable steps should be taken to ensure the confidentiality of participant-specific information.

10. Investigators should take special precautions at all stages of the study if the research has the potential to adversely affect groups of individuals on the basis of race, ethnicity, gender, age, or similar characteristics.

Having established the conceptual basis for decision making regarding human subjects in the occupational health research setting, we will turn our attention to specific topics of interest.

DEFINING HUMAN-SUBJECTS RESEARCH

The first question to answer about a proposed occupational health activity is whether it meets the criteria for research involving human subjects. Personal medical data is often collected in the course of occupational health practice. Certain standards require collection of medical or biological monitoring data for compliance or surveillance purposes. Medical information may also be collected to better define risks in a population or to evaluate interventions. The key to the definition of human-subjects research is the **purpose of the activity**. As defined by the Federal Policy for the for the Protection of Human Subjects, research is "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."[10] Thus, collecting data in order to provide medical care to individuals in the workforce, or to intervene if over-exposure or health effects are detected, is not considered research.

Although this criterion sounds straightforward in the abstract, in practice it often is not. Snider and Stroup discuss several areas of public health practice for which confusion exists with regard to which activities are and are not research, including surveillance, emergency responses, and program evaluation.[21] They propose that the major distinction between research and practice relates to the primary intent for which the activity was designed. The intent of research is to contribute to generalizable knowledge, while the intent of public health practice is to prevent disease and injury and improve the health of communities. Snider and Stroup note that in some cases of public health practice, knowledge gained may be generalized, but that is not the primary intent of the activity.[21]

Determination that an activity does not meet the criteria for human-subjects research does not preclude consideration of issues typically addressed in a human-subjects research protocol. Such activities often require a consent form that addresses all of the issues (where pertinent) that are addressed in consent forms for research studies, including purpose of the investigation, risks and benefits, analyses that will be performed on biological samples, notification of results, permission for storage of unused specimens for future research, etc.

There may be circumstances in which an activity that is not initially research evolves in such a way that it is considered a human-subjects research project. For example, if an analysis of identifiable private information initially collected as part of a public health practice activity is undertaken to generate or contribute to generalizable knowledge, the analysis consititutes human-subjects research and requires IRB review.[7]

PRIVACY AND CONFIDENTIALITY

Both human-subjects research and medical or public health practice conducted in an occupational setting involve issues of privacy and confidentiality. The concept

of personal privacy includes an individual's status (whether or not the information about an individual is known to another) and rights (whether the individual has control over information about him- or herself being shared with anyone else).[27] Confidentiality is a status accorded to information based on a decision, agreement, obligation, or duty such that the recipient of personal data must control disclosure.[27]

For studies conducted by the Federal government, release of records is governed by the Privacy Act[26] and the Freedom of Information Act.[25] The Privacy Act mandates that the government prevent disclosure of information in Privacy Act "systems of records" without consent of the individuals to whom they pertain except under certain conditions, such as in response to a court order. Because there are some situations in which records pertaining to individuals may be released, Federal investigators cannot give study participants the broad assurance that their study records will remain confidential without taking additional steps described below. Instead, the consent form used in NIOSH studies lists circumstances in which data may be released (such as in response to a court order) and states that "aside from these and other . . . no disclosures will be made without your written consent." For specific studies, the consent form may specify that the individual results will not be made available to the company or union, and that in any publications or reports, data will be grouped in such a way that no individual can be identified.

In some studies, the information collected is considered so sensitive that individuals will not consent to participate unless full confidentiality can be assured. In these cases, investigators within NIOSH can request authorization to give assurance of confidentiality under Section 308(d) of the Public Health Service Act.[22] Similar provisions apply for intra- and extramural investigators funded by NIH, who may obtain Certificates of Confidentiality under the authority of Section 301(d) of the Public Health Service Act.[23] State laws also contain requirements to maintain the confidentiality of records of individual study participants.[20]

Occupational health research poses some unique challenges with respect to privacy and confidentiality. Many workplaces or work units are small enough that both management and coworkers may be able to identify individuals by one or more occupational or personal characteristics, such as work assignment and shift, gender, and age. Unlike epidemiological studies in the general population where there are often no records external to the study of the universe of individuals from which participants were recruited, in occupational studies the employer (and sometimes the union) possesses personnel records that include both individual identifiers and characteristics such as date of birth and work history. These records may allow linkage of medical or questionnaire data obtained from the study subject, even if released in unidentified form, to individual identifiers by matching with other data about individuals. Therefore, extra care must be taken in preparing reports and journal articles stemming from occupational studies and in releasing de-identified data files for analysis by other investigators.

For example, in summarizing environmental and biological exposure measurements collected in a manufacturing plant, listing results for each job title by shift may in effect disclose sensitive biological monitoring data for individuals. Even in large mortality studies containing records of thousands of individuals, it is readily possible to match de-identified study files containing demographic, work history, and death information to personnel files by variables such as month and year of birth, and month and year of starting employment, thereby re-linking the cause of death information with individual identifiers. The potential for such linkage is problematic because researchers must agree to maintain the confidentiality of death data they received from the National Death Index and some State Vital Records Offices. When releasing study data to outside investigators (even files with direct identifiers removed), require

their assurance that they will not attempt to link the data with identifiers by indirect means and will not provide the data to others. To further reduce the potential for indirect linkage, consider grouping data rather than providing data on individuals.

When conducting research studies at the work site, it is often difficult to protect the identities of those who are or are not participating in the study. For example, the presence or absence of a sampling pump can be readily observed. Also, if questionnaires or examinations are done on-site, individuals may be observed entering and leaving the examination room. However, investigators are encouraged to make reasonable efforts to protect the identity of participants (e.g., do not post an appointment or sign-up sheet at the worksite or in any other public place). The extent to which precautions are necessary to protect the identities of research study participants will vary in different workplaces. If there is significant concern that participation will result in recrimination, the study may need to be done off-site and off-hours so that participants are unobserved.

When biological monitoring or medical data are collected from individuals, results are provided to the individual participants and to their personal physicians if requested. Release of the results to anyone else requires specific consent by the participant and, in our experience, is relatively rare. Many of the studies in which this has been done involved blood lead measurement. In one such study, the state in which the plant was located had a law requiring mandatory reporting of elevated blood leads. Our consent form specified that elevated blood leads would be reported. In other lead studies, we have offered participants the option of having their blood lead result reported to the company, to satisfy the requirement for periodic blood lead monitoring. In a study conducted in Latin America, the company wished to compare blood lead results between a local lab and the U.S. Centers for Disease Control lab. Thus, in the consent form we explained that the blood lead determinations would be reported to the company with a code number that could be linked to the code number of the sample analyzed locally. In all cases, plans to disclose the data to an outside party were described in the consent form, and where this was an optional component of the study or non-research activity, a separate consent for the disclosure was obtained.

SELECTION OF SUBJECTS, RECRUITMENT, AND INCENTIVES FOR STUDY PARTICIPATION

One of the issues that may arise in selecting subjects for a study is whether there should be **restrictions** based on medical conditions, age, work experience, race, or gender. In some studies, there may be valid reasons for such restrictions. For example, if an investigator is interested in measuring forces related to lifting, he or she may wish to exclude subjects who have a history of hernia or low back pain. Older individuals may be at higher risk of a cardiovascular event with aerobic exertion, and therefore the investigator may wish to set an upper age limit for participation. It may also be desirable, when conducting studies involving specialized equipment or activities, to recruit subjects from among individuals who work with such equipment on a daily basis.

When the IRB reviews **study protocols** that have such restrictions, a number of issues commonly arise. If there is a medical screening component, either by questionnaire or clinical examination, IRB members may raise questions about how well the purpose and nature of the screening is described to the participant in both recruiting materials and the consent document; the adequacy of the screening questions and/or examinations relative to the risks involved; when and how participants will be informed of any abnormal results; and the qualifications of the persons conducting the medical exam and/or making the decision about whether the participant is med-

ically cleared to participate. IRBs may also raise questions about protocols if a specific subgroup of the population is excluded without an acceptable rationale. For example, in a study involving use of heavy equipment, the IRB may question an investigator's plan to exclude women on the grounds that few have the requisite strength, and suggest instead that either subjects be required to have experience operating the equipment in question or that they be required to meet minimum standards with respect to appropriate strength tests.

It is important that subjects being recruited for a study fully understand the circumstances of the study, including: where and when the study will be conducted; how many hours each component will take; any restrictions that will be placed on their activities outside of the examination period, including abstinence from meals, coffee, smoking, or alcohol; whether they will need to remove or wear special clothing or have any sensors or other equipment attached to their body; etc. If there are entry or exclusion criteria for the study that the potential participant can evaluate him- or herself, such as smoking status or pregnancy, these should be stated early in the recruitment process (e.g., in the announcements requesting volunteers). It is also important that workers understand that they are being asked to provide data for a research study as opposed to for routine medical monitoring purposes or reporting requirements.

Payment offered for participation should never be so large as to induce someone who would not otherwise participate to do so.[16] Payment schedules based on time and inconvenience, taking into account average hourly wage of the workforce being studied, travel time to the study site, etc., are often appropriate. Although potential participants may be informed that achieving a high participation rate among the group under study is important to the scientific validity of the result, and that their participation in all the components of the study is necessary for any of their information to contribute (if that is the case), they must also be informed that they are free to withdraw from participation at any time "without loss of benefits to which they may otherwise be entitled." If there is financial compensation involved, the consent form should state what will happen to their compensation if they choose to withdraw from the study before completing all of the study requirements. Generally, participants who withdraw should receive at least a prorated portion of the renumeration.

NOTIFICATION OF INDIVIDUAL MEDICAL OR BIOLOGICAL TEST RESULTS AND OVERALL STUDY RESULTS

It is important to distinguish conceptually between notification of individual test results and notification of overall study results. There is little debate that subjects should be notified of individual results for tests that are clinically relevant. Notification of test results that do not have clinical interpretation is more controversial. The general concept of "right to know" and ethical concerns surrounding the Tuskegee study, in which important health information was withheld from study participants,[12] have motivated some researchers to disclose *all* test results, even if they are experimental in nature. On the other hand, especially with respect to studies involving genetic characteristics, there are increasing concerns that individuals might be subject to discrimination based on genetic traits, and thus notification of results on genetic traits may carry some risk. A possible middle ground is to offer study participants the option of receiving their test results, along with a discussion of the risks and benefits.

In some studies, biological monitoring is done that, while having no direct clinical interpretation, may be related to an exposure standard or guideline. Even where there is no exposure standard or guideline, reporting the participant's result along with the group range may provide the participant with information about his or her occupational exposure. Such an approach is illustrated in Figure 1. In studies where

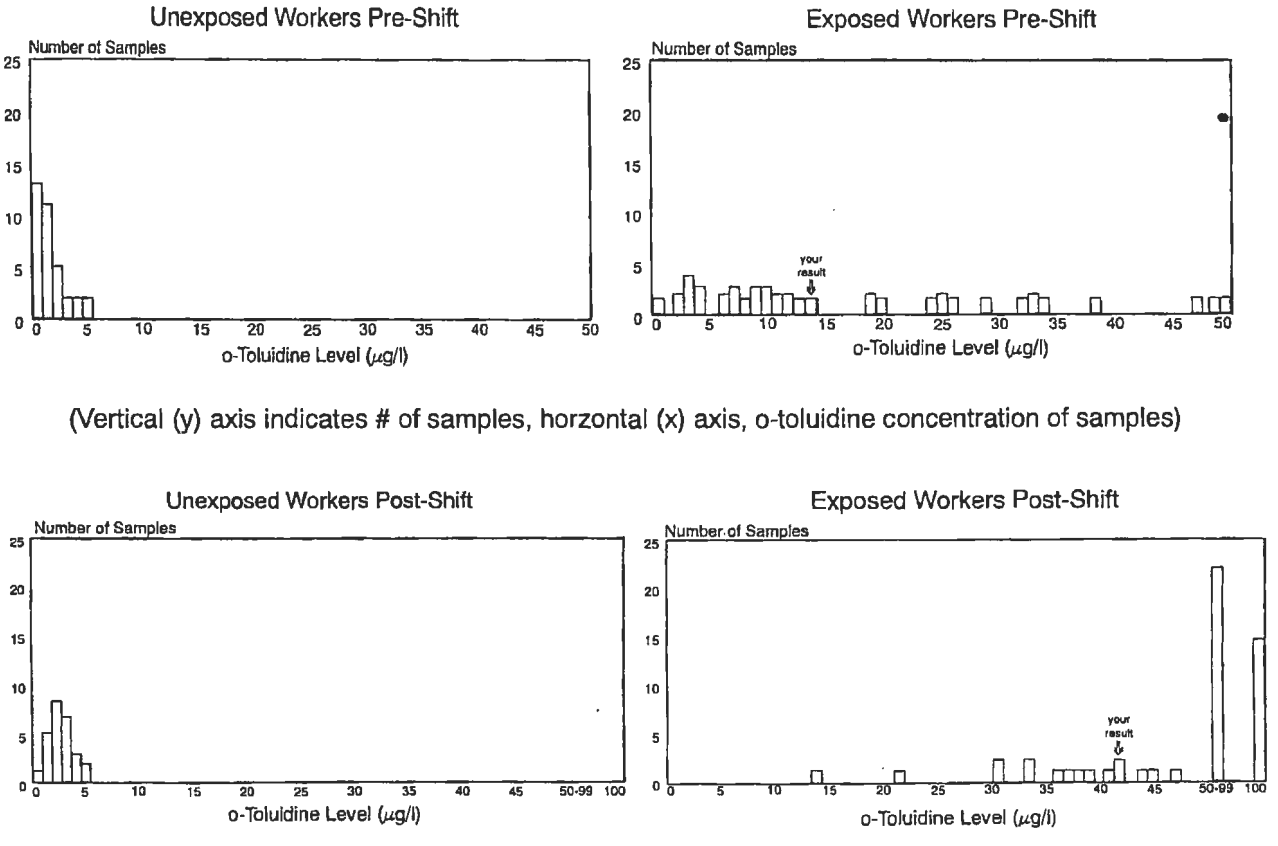

FIGURE 1. Urinary o-toluidine levels among unexposed and exposed workers: where your results fall.

medical tests with established clinical norms or tests relating to exposure guidelines are performed, the laboratory or examination results should be reviewed immediately to discern any out-of-range values that would require repeat testing, exposure intervention, or referral to a physician.

NIOSH has a policy that individuals involved in participatory research studies should be notified about the overall study findings. NIOSH also has a policy that for non-particpatory epidemiologic studies such as cohort mortality studies, individual subjects will be notified of results if the results exceed a specified threshold of risk.[19] Notification of overall study results is generally done via a short letter with fact sheets. The fact sheets often contain a short summary of the study's purpose and main findings, as well as recommendations for screening or other measures that workers can take to protect their health. These materials are geared to an eighth grade reading level.

A difficult study finding to convey is when the group results show a difference in a clinical outcome related to exposure, but all of the values are in the clinically normal range. For example, in a study of reproductive function in a group of men employed in the manufacture of a whitening agent precursor with estrogenic properties, the hormone testosterone was found to be decreased in the exposed group, but all of the values were in a clinically normal range. This was expressed as follows:

> *"A wide range of levels of the hormone testosterone are considered normal. No man in the study had lower testosterone levels than normal. However, more [exposed] workers were in the lower part of the normal range than the comparison workers. There seemed to be a connection between working in the [exposed] area and lower testosterone levels, even though the results were in the normal range."*

Notifications of overall study results should almost always contain public health recommendations when a study has found an association between an occupational exposure and an outcome. These public health recommendations include information concerning exposure standards and guidelines and methods to reduce exposure (if the process or plant under study continues to be operating), as well as steps that the individual can take to protect his or her health. These steps may include learning about symptoms of the disease of concern, regular screening, or reduction of non-occupational risk factors such as cigarette smoking. An example of a recent notification brochure is shown in Figure 2.

ANALYSIS AND BANKING OF BIOLOGICAL SPECIMENS

Ethical and policy considerations in research involving human biological materials were considered by the National Bioethics Advisory Commission (NBAC).[13] The Commission recommended that when human biological materials are collected, whether in a research or clinical setting, it is appropriate to ask subjects for their consent to store samples for future use, even in cases where such uses are at the time unknown. They further recommended that when obtaining consent for the research use of human biological materials, efforts should be made to be as explicit as possible about uses to which the material might be put and whether it is possible that the research might be conducted in such a way that the individual could be identified. The NBAC also recommended that for samples collected before informed consent procedures for storage were implemented, IRB review be required if the samples can be linked with identifiers, even if the investigators performing the research do not have access to the identifiers. Depending on the circumstances, investigators may be required to obtain individual consent for research involving the samples, may be permitted to analyze the samples provided that they are rendered anonymous, or may be

Hello!

In 1998, you participated in a study of termiticide applicators who applied chlorophyrifos-containing insecticies (Dursban, Equity, Cyren) to kill termites. We already sent you your own result (please contact us if you did not receive these results). This pamphlet describes the overall results of the study.

What did we find?

NIOSH found the following results when comparing termicide applicators who applied chlorpyrifos to those persons in a comparison group who were not termiticide applicators:

- The applicators did not differ significantly from the comparison group for any test in the clinical exam.
- The applicators did not differ significantly from the comparison group for most of the 40 sub-clinical tests. The applicators performed significantly worse, however, on the pegboard turning (hand flexibility) and postural sway (body movement with eyes closed) tests.
- The applicators reported significantly more symptoms than the comparison group. These symptoms included memory problems, emotional states, fatigue, and loss of muscular strength.
- The eight applicators reporting having been poisoned by chlorpyrifos scored significantly lower on many of the clinical and sub-clinical tests than the comparison group.
- We did not find any effect of being in one genetic group or another.

Why did we do the study?

In 1998, NIOSH conducted a variety of tests on the nervous system from 2 groups of persons. One group consisted of termicide applicators who applied chlorpyrifos-containing insecticides to kill termites. The other group did not work with chlorpyrifos and was used as a comparison group.

We checked the neurologic function in each person by

- conducting clinical exams of the nervous system who performed two neurologists. The exam consisted of observation of eye movement, tremor coordination, muscle tone, strength, sensation, and reflexes.
- conducting over 40 sub-clinical tests of nerve conduction velocity, arm/hand tremor, sensitivity to vision, smell, motor skills, or skills of memory and attention span.
- looking at the level of TCP, a break-down product of chlorpyrifos, in the urine.
- performing the genetic test to see if some people are most susceptible to neurologic effects of chlorpyrifos

Remember what we found:

- Applicators had no clinical effects on the medical exam compared to non-applicators.
- Applicators had few differences on sub-clinical tests compared to non-applicators.
- Applicators had more self-reported symptoms compared to non-applicators.
- Applicators who reported past poisoning scored lower on many tests. Applicators should take every effort not to accidentally be exposed to a large amount of chlorpyrifos.

FIGURE 2. An example of a NIOSH Worker Notification Brochure.

permitted to analyze the samples even though *not* rendered anonymous, with the consent requirement waived.

The NBAC also recommended that to facilitate collection, storage and appropriate use of human biological materials in the future, **consent forms** should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decisions they are about to make. Such options might include, for example: (a) refusing use of their biological materials in research; (b) permitting only unidentified or unlinked use of their biological materials in research; (c) permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies; (d) permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies; (e) permitting coded or identified use of their biological materials for the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies; (f) permitting coded use of their biological materials for any kind of future study.

At the time a biological sample is collected, it is important to disclose to the study subject what tests will be done on the sample. We often state in our consent forms that the samples will not be tested for drugs, alcohol, or HIV, because that is a frequent concern of participants. Even when there is no intent to preserve samples for future analysis or conduct additional tests for research purposes, there is often sample remaining after the initial analysis is done. Frequently, **left-over sample** is placed in storage on a temporary basis so that analyses can be repeated in the event of quality-control problems. Once collected and stored, it is tempting to use such samples for research not specified in the original consent form. It is important to think through possible uses and retention for future research of biological samples in advance of collecting them, so that proper consent procedures can be followed.

When the investigator has no intention of preserving the sample and using it for other purposes, it is appropriate to state in the consent form that the samples will be disposed of once the analyses are completed. If there is a desire to preserve the sample for possible use in future analyses, this should also be stated in the consent form, and as described above, there should be a separate consent regarding the storage and future analysis of the specimen. Investigators should consider whether the stored samples will be coded (with identifiers preserved) or de-linked from identifying information, so that these issues are addressed in the consent form.

One consideration in **de-linking** is that there is no option to notify subjects of individual test results in the future if they have clinical significance. An additional concern about de-linking is the loss of information needed to interpret results. For example, in an attempt to evaluate latex antibody prevalence among occupational groups other than healthcare workers, de-linked blood samples from a number of occupational cohorts were analyzed. However, when it was found that one of the occupational groups studied had a higher prevalence of latex antibodies than the others, it was impossible to determine whether this might be related to cross-reactivity with a protein antigen measured in the original study, since the latex antibody results for individuals could not be linked with the antibody results for the protein antigen.

Some of the more important uses of stored specimens may be difficult to visualize when seeking consent or determining what data should be maintained in association with stored samples. One option that may be considered is to retain information (such as exposure variables) in such a way that it cannot be used to link back to the original study data and thus disclose the identity of subjects. This might be done, for example, by recoding a continuous variable into a categorical one with a limited

number of categories. Thus, the subject is protected from future potential harm if test results are disclosed. If the findings are of clinical importance, the investigator studying de-linked samples can notify *the population* of the *overall* results, so that individuals can arrange to be tested if they want more information. This approach has the added advantage of moving the individual from a research subject role to a private patient role, for which follow-up counseling and tailored medical care is more appropriate. Investigators should realize that notification is a substantial commitment, as they will need to track addresses of study subjects for notification purposes.

STUDIES INVOLVING GENETIC MODIFIERS OF RISK

In the occupational setting, genetic factors may be considered as potential modifiers of the relationship between exposure and disease. With respect to occupational cancer, there are a number of exposures that may be modified by cancer susceptibility genes. For example, risk of bladder cancer associated with aromatic amines may vary depending on NAT1 and NAT2 status, and risk of leukemia associated with benzene may be influenced by CYP2E1, NQO1, and MPO.[15] Genetic factors may also play a role in hypersensitivity disorders, such as chronic beryllium disease (CBD), which has been associated with HLA-DPB1 alleles that contain glutamine at position 69 in up to 97% of individuals with CBD, but also 30–40% of controls.[14]

It is important to recognize the distinction between "mutations that have a high known risk of disease" and "genetic polymorphisms that involve common alleles that are neither necessary nor sufficient for the development of disease, many of which are risk factors only in combination with particular environmental exposures or lifestyle factors."[11] Most genetic markers considered in occupational studies are in the latter category. Incorporating **genetic polymorphisms** into epidemiologic studies in occupational groups has the potential to increase understanding of the relationship between occupational exposure and disease by: (1) offering insight into the mechanism of action of the disease-causing agent; (2) potentially allowing for detection of a risk associated with low exposures in a susceptible subgroup that would not be detectable in a genetically heterogeneous population. Occupational groups are well suited to studying the association between genetic polymorphisms and environmental exposures because worker exposures tend to be higher and better-documented than those in the general population. However, the investigator conducting such studies needs to be aware of a number of ethical issues.

Earlier in this article, we discussed the principles underlying human-subjects research. Almost all of these principles have generated concern about conducting genetic studies in the workplace.[17] There are, in addition, specific concerns about economic and social ramifications of genetic testing. Worker advocates fear that genetic testing will result in discriminatory hiring practices and reduced efforts to minimize exposure to toxic substances. Current employees may fear that genetic testing in a research study will reveal a risk factor to the employer and induce job loss or reassignment.[1] There is even concern that mere acknowledgment on an employment or insurance application that they may have had a biological or genetic test may result in denial of employment or insurance.[18]

Consideration of genetic markers in epidemiologic research studies is directed towards characterizing interrelationships between the genetic marker and exposure; for example: Is there an effect of the exposure in either of the genotype strata? Is the effect of exposure in one genetic stratum different from the effect of exposure in the other stratum? Even when a genetic marker has been replicated in a number of studies to modify an exposure-disease association, it is generally only one of a number of predictors in a complex, multi-factorial pathway, most of which is unknown. The risk

associated with the genetic marker in the group may be difficult to apply to the individual, especially when the role of other genetic polymorphisms has not been well investigated. Thus, the group results should be used cautiously, if at all, in "individual risk assessment." This creates considerable difficulty in determining when individual results of genetic polymorphisms have sufficient clinical significance to be reported to study subjects, and in crafting the language of that notification. The same issue would argue against the use of genetic markers in employee placement decisions, given the current state of knowledge on most markers.

One of the main issues concerning Institutional Review Boards (IRBs) with respect to research on genetic polymorphisms is whether and **when to report the results to study participants**. Many argue that when there is no well-documented clinical interpretation, the potential harm of notifying the subject exceeds any benefit, and that subjects should be asked to participate in the study under the condition that they will *not* be informed of the result. For many genetic polymorphisms involved in occupational studies, their selection for study implies that the investigator suspects they may modify the exposure-disease relationship; this suspicion may be based on mechanistic reasons or a finding in an earlier study. Knowledge of the role of the genetic polymorphism with respect to the specific exposure-disease relationship, as well as possibly other unrelated exposure of diseases, is rapidly evolving. Depending on one's philosophical perspective, as well as on the strength of the exposure-disease relationship and other scientific considerations, the investigator may choose *not* to provide the study subject with individual results because the future implications with respect to disease risks, insurance discrimination, etc., are unknown, or may *leave open the opportunity* for study subjects to receive their results in the future if later findings document that they have clinical implications.

There is a considerable burden on the investigator who chooses to provide workers with their individual results to accurately communicate the probabilistic and speculative nature of the genetic analysis. Workers "testing positive" may assume a fatalistic approach to their work environment and may eschew recommended prevention actions, and those "testing negative" may assume a false immunity. Both situations would adversely influence the individual's perception of, and adherence to, safe work practices.

Guidelines and an **informed consent template** that are appropriate for population-based studies of low penetrance gene variants have recently been published.[4] The guidelines and template are directed at the common situation in which the study is not expected to yield clinically relevant information, but they do recognize that at some point the weight of evidence for a gene-disease association or a gene-environment interaction will mean that the next round of epidemiologic studies will be confirmatory rather than exploratory. Breskow et al. recommend that when the risks identified in a study are both valid and associated with a proven intervention, then disclosure may be appropriate.[4] They suggest that at the outset of the research, investigators make an assessment of whether results are likely to generate information that could lead directly to an evidence-based intervention. If investigators believe that this is likely based on existing evidence, they should plan to report individual results, and the analyses must be performed under Clinical Laboratory Improvement Amendments (CLIA) certification, which establishes criteria for quality assurance. Laboratories that assay human specimens in context of epidemiologic studies, but do not report patient-specific results for the purpose of diagnosis, prevention, or treatment, do not usually request CLIA certification of a specific test or assay.

In NIOSH field research studies, regardless of whether human-subjects issues are involved, we follow tripartite procedures in which union and management representatives are informed about the purpose and findings of site visits and have the opportu-

nity to participate in a review of study protocols and final reports. For studies involving genetic factors or other highly sensitive issues, it is especially important to have input from worker representatives both on the procedures to be followed and on the understandability of materials describing the study to potential participants. It is also desirable to seek advice from experts who are not involved in the study on difficult ethical questions such as the risks and benefits of notifying study participants of their individual genetic results, as well as interpretation of risk information to study subjects.

EVALUATION OF RISKS IN OCCUPATIONAL HEALTH RESEARCH

Human-subjects regulations distinguish between minimal risks and greater than minimal risks. The Federal regulations governing human-subjects research specify procedures that are considered to involve no more than **minimal risk**. In occupational studies, these minimal-risk procedures typically include collection of blood samples within specified limits and collection of data through noninvasive procedures routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Studies involving no more than minimal risk are eligible for expedited review, i.e., they can be reviewed by one or more members of the IRB and do not require a convened full-board review. Studies qualifying for expedited review are held to the same standards of subject protection as those requiring full-board approval. Studies involving **greater than minimal risks** require higher levels of consideration and documentation by the investigator.

While IRBs have diverse membership, members may not have the specific expertise to evaluate the risks associated with a specific procedure. If an investigator is proposing to subject individuals to a procedure with potential adverse consequences, the study protocol should specifically address these consequences and the probablility of occurrence, based on the literature. The investigator should also address the issue of whether there are alternative procedures that could yield the same benefit, but with lower risks to participants.

In studies with more than minimal risk, the IRB is likely to look even more carefully at risks versus benefits of the study, and the assessment of benefits may include issues about the scientific validity of the study and whether it is likely to yield the intended benefit. It is often desirable to document for the IRB that such studies have had scientific peer review and that the peer reviewers have specifically addressed whether the risks of the procedures have been accurately described and are justified based on the potential benefits. The IRB will also consider whether appropriate precautions have been taken to minimize the risks. For example, in a study involving cardiovascular exertion, it may be desirable to select individuals within a certain age range, or to exclude individuals with certain medical conditions, to minimize the likelihood of an adverse event. It is important to document in the protocol the procedures and criteria that will be used for medical exclusion.

For all studies, there should be a written emergency plan, including procedures to be followed in the event of illness or injury in a study participant. For studies involving more than minimal physical risk, the emergency care plan should be commensurate with the level of risk. For example, in some cases studies should only be done in a clinical setting, with a physician available or on call.

THE WORKPLACE AS A CLOSED COMMUNITY

In contrast to broad-based population research or clinical trials in which participants may have no knowledge of one another prior to, during, or after the research, workplace studies take place within a closed community. This means that study par-

ticipants have a past history of relationships and associations with one another apart from their involvement in the study. Therefore, issues such as recruitment, informed consent, and data management pose unique challenges. Overzealous managers or union representatives may feel compelled to "turn out the numbers" and may apply subtle pressures on individuals to participate. Workers themselves may feel obligated to participate to be a good team player or to avoid any perceived repercussions for not going along with the study.

Investigators must take extra precautions to make sure that the key players within the organization understand the importance of *voluntary* participation and that the recruiting process is free of any bias or coercion. This should be stressed in planning and study review meetings prior to initiating recruitment. Recruiting materials, announcements, scripts, and similar informational materials about the study should be carefully developed to present a balanced perspective of the purpose, risks, benefits, and voluntary nature of the research. As a means of minimizing and assessing coercive influences, the consent form should list the name and phone number of a point of contact on the reviewing IRB who can receive anonymous complaints or inquiries about the ethical conduct of the study.

If the study involves accessing employee records, company employees who maintain these records may be involved in data access, transcription, and aggregation. Depending on the nature of the study, these employees may uncover information about a fellow worker that they would not have normally have reviewed, or they may learn additional information about an individual while integrating different data sets unique to the study design. The investigators need to be sensitive to these issues in developing their data collection and data management plan to insure that company employees do not have access to personally identifying information that is outside their normal range of responsibilities.

THE CONSENT FORM

In reviewing human-subjects research protocols, IRBs pay very close attention to the consent form. The Federal regulations pertaining to human-subjects research specify what elements have to be addressed in obtaining informed consent.[10] Issues that are paramount in the consent process include whether the consent form accurately and clearly describes the purpose of the research, what participation involves, and the potential risks and benefits to the individual and society. If study procedures or testing equipment is unusually difficult to explain, the IRB may suggest that investigators develop a video that participants can view prior to consenting. The following are some issues that IRB members are especially sensitive to and/or that arise frequently in reviewing consent forms for occupational studies:

- Consent forms should not imply more of a benefit to individual participants than truly exists. For example, if a very limited medical screening is to be done for potential participants, it is questionable whether "a free medical exam" should be listed as a benefit of the study.
- Payment for participation is considered as a compensation for time and inconvenience. It should not be listed as a benefit of participation.
- All the potential risks of participation should be carefully described and be consistent with the risks documented in the protocol.
- If a questionnaire is to be administered, the consent form should state what information will be covered in the questionnaire, especially any sensitive information that may be requested.
- If biological specimens are to be collected, either all of the tests to be conducted should be described, or explicit consent should be obtained for unrestricted

use of the specimens. Similarly, if samples are to be stored for future analyses, specific consent should be requested. The consent form should also state whether samples will be stored in an identifiable or anonymous form, whether the subject will be informed of individual test results, and when that notification is expected to occur.

- Especially if the study involves a large number of clinical tests, increasing the probability that some participants will be outside the normal range, it may be desirable to mention this as a risk of participation, e.g., "*One disadvantage, besides the slight discomfort and inconvenience described above, is that a test result may be outside the range of 'normal' even though nothing is wrong. This could result in a recommendation for further medical evaluation that, ultimately, may not have been necessary.*"
- It should be specified who will be responsible for emergency treatment and other medical costs in the event that a person is injured as a result of participation.
- Confidentiality procedures for data collected in the study should be described.
- The name and phone number of the principal investigator as well as the IRB chair should be included in the consent form.
- Both the investigator and the study participant should retain a copy of the signed consent form.

The Centers for Disease Control and Prevention has made available, on its public website, a reference for developing consent forms and oral scripts (www.cdc.gov.od/ads/hsrconsent). This document may provide a useful resource for investigators since it contains sample language for many common situations, such as explaining the risks associated with venipuncture. Finally, it must be remembered that informed consent is a continuing process that extends beyond the written document. Study participants may have a variety of questions and concerns that are not anticipated in the consent form and which may influence their decision to enroll or to continue in study. New risks may be identified based upon this research or other information reported in the literature. Investigators must be prepared to dialogue with study participants *throughout the study* about issues *as they arise* to assure that workers' decisions to participate remain informed and current.

CASE STUDY

Investigators are planning to conduct a study that will compare the level of stable chromosomal aberrations in peripheral lymphocytes in a group of individuals with long-term occupational radiation exposure, to a demographically similar group with no occupational radiation exposure. Stable chromosomal aberrations will be measured using fluorescence *in situ* hybridization (FISH). Radiation exposures in the "exposed" group were within occupational limits based on U.S. regulations. Although the relationship between chromosomal aberrations and radiation has been studied in a number of populations, there have been relatively few studies employing the FISH technique, and the characteristics of the radiation in this particular study population differed from that observed in other occupational settings. The primary purpose of the study is to evaluate the exposure-response relationship between the radiation exposures present in this occupational setting and chromosomal aberrations.

Investigators are aware that genetic factors, including genetic variability in DNA repair, may modify the exposure-response relationship. Therefore, the investigators wish to examine the potential modification of the exposure-response relationship by genetic factors. However, since research involving DNA repair genes and other genetic factors that may influence the exposure-response relationship is rapidly evolving, the investigators do not wish to specify at the time of blood collection which genetic factors will be measured.

Both the radiation-exposed population under study and the control group comprise college-educated professionals. Recruitment will be restricted to non-smokers aged 35 to 50. Subjects will be pre-screened to exclude individuals with genetic disorders associated with elevated chromosomal aberration frequency and those with medical radiation or other exposures likely to induce chromosomal aberrations.

Controversies

1. Should study subjects receive their individual chromosomal aberrations results?

In favor of notification:

Chromosomal aberration (CA) frequency is a well-understood biological marker that is associated with both radiation exposure and risk of disease. Quite recently, an increased risk of cancer in healthy individuals with high levels of chromosomal aberrations has been documented.[5] In one study that was able to control for smoking and occupational exposure to carcinogens, significant increases in risks of cancer (about 2.5 fold) for high versus low levels of CA were found.[5] The risk for high versus low levels of CAs was similar in subjects heavily exposed to carcinogens and in those who had never, to their knowledge, been exposed to any major carcinogenic agent in their lifetime, supporting the idea that chromosomal damage itself is involved in the pathway to cancer.

The investigators had previously conducted several studies using CAs as an endpoint and, in accordance with their agency's policy at the time, had notified individuals of their CA results. They were not aware of any problems or adverse consequences of these notifications.

The study group is highly educated and one of their motivations to participate may be interest in obtaining their individual results. Subjects may decline to participate if they are not provided their individual result.

Opposed to notification:

Although some studies have found a 2.5 fold, statistically significant, increased risk of cancer associated with high versus low chromosomal aberration frequency, it is unclear how this applies to an individual because so much of the risk of cancer is unexplained. It is not clear that there is any intervention that would decrease morbidity and mortality in the higher-risk group, since for many of the major cancers there is no well-accepted screening test. The subjects are already non-smokers, so this general public health advice to decrease cancer risk would not be applicable.

It is very hard to document adverse social or economic consequences, such as discrimination in employment or health insurance, to individuals whose CA results fall in the upper range of population norms. However, there is justifiable concern that as evidence increases that those with elevated CAs have increased risk of cancer, CA frequency may used (or misused) in ways that would have a negative impact on the individual.

Resolution:

At the conclusion of the study, subjects will be offered the option of receiving their individual CA results. The option was deferred until the end of the study because to an extent the benefits and risks of receiving the results will differ based on the overall findings. For example, if a strong association is found between radiation exposure and CA frequency in this study, subjects may feel that obtaining their individual result is more meaningful than if no association is found. On the other hand, if a small number of individuals are found to have a very high elevation in CAs, then the risk of receiving the results may be higher, at least for those individuals with the high values.

2. The investigators wish to store blood samples for future, unspecified genetic analyses. Should the IRB require that these samples be de-linked to protect subjects

from potential risks of such analyses, since their scope cannot adequately be defined for the purposes of consent?

In favor of maintaining the link:

Since the primary purpose of the genetic component of the study is to determine whether the genetic factor influences the exposure-response relationship, it is important to retain detailed information about radiation exposure, potential confounding factors, and CA results for the later phase of the study which incorporates genetic information. Thus, completely de-linking the stored samples would not allow them to be used for the purpose intended. Even if data are substantially re-coded (e.g., a continuous exposure variable would be converted into a categorical variable with relatively few categories), it will be difficult to eliminate the possibility of indirect linkage through variables common to both the original data set and the de-linked data set.

Although there is grave concern about possible economic consequences associated with obtaining results from research studies incorporating genetic markers, evidence that this has occurred is very limited. Much of the concern about the sensitivity of genetic studies stems from studies of familial aggregation which involve high penetrance genes; these concerns are not relevant to population studies involving common genetic polymorphisms. It is unlikely that any of the genetic polymorphism results will have clinical implications. Therefore, a viable alternative would be to maintain the link between the biological samples and the original study data, thus maximizing the ability to examine modification of the exposure-response relationship by genetic factors, but to inform study subjects on the Consent For Stored Samples form that their individual results will not be reported to them.

In favor of breaking the link:

Since the investigators can't specify which genetic factors they will examine, the extent of the potential risk to subjects is unclear. If one or more of the genetic factors is found to have a strong relationship to a disease, or if there is a strong gene-environment interaction, disclosure of this information would put certain subjects at high risk of discrimination. Since the study is being done by a Federal Agency, there are certain conditions under which individual data can be released. Thus, even if individual results are not provided to study subjects, it may not be possible for investigators to protect them from disclosure.

Resolution:

The investigators will de-link the original study data from the stored blood samples to be used in the genetic analysis. This will be done after the analysis of the original study is complete, but before any genetic analyses are conducted. The reason this will be done after the study is complete is that the investigators will use information from the original study, such as the distribution of CA frequencies and knowledge of which covariates are significant in the statistical model, to determine which data need to be retained for the analysis of genetic factors and how it can be re-coded so that the possibility of linking back to original identifiers is eliminated. The investigators have agreed to present this plan to their IRB prior to proceeding with the genetic analyses.

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