Executive Summary

ABSTRACT

Some of the polio vaccine administered from 1955-1963 was contaminated with a virus, called simian virus 40 (SV40). The virus came from the monkey kidney cell cultures used to produce the vaccine. Most, but not all, of the contamination was in the inactivated polio vaccine (IPV). Once the contamination was recognized, steps were taken to eliminate it from future vaccines. Researchers have long wondered about the effects of the contaminated vaccine on people who received it. Although SV40 has biological properties consistent with a cancer-causing virus, it has not been conclusively established whether it might have caused cancer in humans. Studies of groups of people who received polio vaccine during 1955-1963 provide evidence of no increased cancer risk.

However, because these epidemiologic studies are sufficiently flawed, the Institute of Medicine's Immunization Safety Review Committee concluded that the evidence was inadequate to conclude whether or not the contaminated polio vaccine caused cancer. In light of the biological evidence supporting the theory that SV40-contamination of polio vaccines could contribute to human cancers, the committee recommends continued public health attention in the form of policy analysis, communication, and targeted biological research. See Box ES-1 for a summary of all conclusions and recommendations.

Immunization to protect children and adults from many infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school, college, or day care, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader societal significance of these immunization safety issues. While all the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group.

The committee reviews three immunization safety review topics each year, addressing each one at a time. In this fifth report in a series, the committee examines the hypothesis that exposure to polio vaccine contaminated with simian virus 40 (SV40), a virus that causes inapparent infection in some monkeys, can cause certain types of cancer.

The committee is charged with assessing both the scientific evidence regarding the hypotheses under review and the significance of the issues for society.

- The *scientific* assessment has two components: an examination of the epidemiological and clinical evidence regarding a possible *causal relationship* between exposure to the vaccine and the adverse event, and an examination of theory and experimental evidence from human or animal studies regarding biological *mechanisms* that might be relevant to the hypothesis.
- The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event. Other considerations may include the perceived intensity of public or professional concern or the feasibility of additional research to help resolve scientific uncertainty regarding causal associations.

The findings of the scientific and significance assessments provide the basis for the committee's recommendations regarding the public health response on the issue. In particular, the committee addresses needs for a review of immunization policy, for current and future research, and for effective communication strategies.

For its evaluation of the hypothesis relative to SV40-contaminated polio vaccine and cancer, the committee held an open scientific meeting in July to hear presentations on issues germane to the topic. The presentations to the committee at the open meeting are available in electronic form (audio files and

slides) on the project website (www.iom.edu/imsafety). In addition, the committee reviewed an extensive collection of material, primarily from the published, peer-reviewed scientific and medical literature. A list of the materials reviewed by the committee, including many items not cited in this report, can be found on the project's website.

THE FRAMEWORK FOR SCIENTIFIC ASSESSMENT

Causality

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by previous IOM committees (IOM, 1991, 1994), convened under the congressional mandate of P.L. 99-660 to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The committee does not conclude that the vaccine does not cause the adverse event merely if the evidence is inadequate to support causality. Instead, it concludes that the "evidence is inadequate to accept or reject a causal relationship."

Biological Mechanisms

Evidence considered in the scientific assessment of biological mechanisms[1] includes human, animal, and *in vitro* studies related to biological or pathophysiological processes by which immunizations could cause an adverse event. When other evidence of causality is available, biological data add supportive evidence but cannot prove causality on their own.

The committee has established three general categories of evidence on biological mechanisms:

[1] For a discussion of the evolution of the terminology concerning biological mechanisms, see the committee's earlier reports (IOM, 2001a,b, 2002a,b).

1. Theory only. A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and that does not contradict known physical and biological principles, but it has not been demonstrated in whole or in part in humans or in animal models.
2. Experimental evidence that the *mechanism operates* in animals, *in vitro* systems, or humans. Experimental evidence often describes effects on just one or a few of the steps in the pathological process required for expression of disease. Showing that multiple components of the theoretical pathways operate in reasonable experimental models increases confidence that the mechanisms could possibly result in disease in humans.
3. Evidence that the *mechanism results in known disease* in humans. For example, the wild-type infection causes the adverse health outcome, or another vaccine has been demonstrated to cause the same adverse outcome by the same or a similar mechanism

If the committee identifies evidence of biological mechanisms that could be operational, it will offer a summary judgment of that body of evidence as weak, moderate, or strong. The summary judgment of the strength of the evidence also depends on both the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence.

SV40 Contamination of Polio Vaccine

The tissue cultures used to grow poliovirus for the vaccines in question came from kidneys of rhesus and cynomolgus macaques.[2] In 1960, Sweet and Hilleman (1960) reported that these tissues could be infected with SV40, a previously unknown virus that commonly infects rhesus macaques. SV40 is a member of the polyomavirus family[3]. Soon after its discovery, SV40 was shown to be able to produce tumors in hamsters and to transform human cells in culture (Eddy et al., 1961, 1962; Girardi et al., 1962; Koprowski et al., 1962; Shein and Enders, 1962a,b). Testing confirmed that some of the tissue cultures used in producing inactivated polio vaccine (IPV) and oral polio vaccine (OPV) were contaminated with SV40. In 1961, the U.S. government established require-

[2] Current formulations of IPV and OPV available in the United States are required by the FDA to be free of SV40. The IPV produced today uses poliovirus grown on Vero cells, a continuous line of green monkey kidney cells. OPV is no longer produced in the United States, but as the recommended vaccine to control polio outbreaks, a stockpile of OPV is available for these purposes (CDC, 2000). The OPV was produced in the United States in monkeys raised in colonies free from SV40 or grown in Vero cells and was screened for viruses, including SV40 (Sutter et al., 1999).

[3] Polyomaviruses generally cause inapparent infection in the natural host but can cause disease in non-host species or in immune-compromised hosts. Two other human polyomaviruses are known as JC and BK.

ments for testing to verify that all new lots of polio vaccine are free of SV40 (Egan, 2002). Potentially contaminated vaccine from previously approved lots of IPV was not recalled, however, and might have been used until early 1963.

IPV administered between 1955[4] and 1963 to about 98 million children and adults is assumed to be the primary source of human exposure to SV40 in the United States.[5] In addition, experimental lots of OPV contaminated with SV40 are known to have been administered to about 10,000 people participating in clinical trials between 1959 and 1961. Tests of stored samples of the IPV that had been administered in the United States from May through July in 1955 found varied levels of SV40 contamination, with some vaccine showing no contamination (Fraumeni et al., 1963). From these data, Shah and Nathanson (1976) estimated that 10% to 30% of IPV contained live SV40 and that similar percentages of the approximately 98 million Americans who had been vaccinated by 1961 were exposed to SV40.

While it is certain that many people were directly exposed to SV40 through injections of IPV, two related matters remain unresolved. First, it is possible that some portion of the population might have been exposed to SV40 before IPV was introduced (Geissler et al., 1985; Shah et al., 1972). Second, it is unclear whether the SV40 received through the vaccine could be transmitted within the population once the contaminated vaccine was no longer in use.

SCIENTIFIC ASSESSMENT

Causality

For its review of the epidemiologic evidence on the association between exposure to polio vaccines containing SV40 and the subsequent development of cancer, the committee found studies examining cancer incidence or mortality. Also included in the committee's review are studies of cancers occurring in children who may have had a prenatal exposure to SV40 through vaccination of their mothers.

The available studies are reviewed in the following three categories: cancer incidence, cancer mortality, and cancers following prenatal exposure to SV40-containing vaccine. For cancer incidence, the committee reviewed five ecologic studies (Fisher et al., 1999; Geissler, 1990; Olin and Giesecke, 1998; Strickler et al., 1998; Strickler et al., 1999) and two controlled observational studies (Innis 1968; Stewart and Hewitt, 1965). For cancer mortality, the committee reviewed two ecologic studies (Fraumeni et al., 1963; Strickler et al., 1998) and one un-

[4] IPV was licensed and widely distributed in 1955, however exposure to SV40 may have also occurred in the 1954 field trial of IPV.

[5] During the same period, SV40 also contaminated an experimental respiratory syncytial virus vaccine given to about 100 adults and a licensed adenovirus vaccine given to about 100,000 military inductees (Shah and Nathanson, 1976).

controlled observational study, including two follow-ups to the study (Carroll-Pankhurst et al., 2001; Fraumeni et al., 1970; Mortimer et al., 1981). For cancers following prenatal exposure to SV40-containing vaccine, the committee reviewed two controlled studies (Farwell et al., 1979; Heinonen et al., 1973). The majority of the studies showed no increase in cancers.

All of the studies that the committee reviewed concerning cancer incidence or cancer mortality and exposure to polio vaccine containing SV40 have substantial limitations. Many of these studies were ecologic in design. In an ecologic study, the unit of analysis is a group. Because data on exposure and disease are available only on a group level, it is difficult to make causal inferences regarding the association between an exposure and disease at the individual level (Kleinbaum et al., 1982).

Most of the epidemiologic studies on polio vaccine containing SV40 and cancer are subject to misclassification bias because they rely on year of birth to designate exposure status. Even though polio vaccine known to contain SV40 was in use from 1955 to 1963, it is difficult to accurately determine which individuals received the vaccine without having access to individual vaccination records. The studies may also be subject to misclassification bias because of a lack of detailed and specific information about the presence of SV40 contamination in individual vaccine doses. In addition, the assumption that persons who received polio vaccine after 1963 were unexposed to SV40 may not be accurate if sources of exposure other than contaminated IPV exist.

The studies were also limited by the rarity of the tumors thought to be associated with exposure to SV40. The effect estimates calculated from a small number of tumors are more sensitive to distortion from confounders, bias, and chance. The cohort exposed to contaminated vaccine has not yet reached the age when the cancers of interest are of high incidence, so these associations in particular cannot be ruled out by the evidence to date. Studies of cancer mortality are also subject to confounding due to improvements over time in the effectiveness of treatments, which may produce a decline in mortality rates that is unrelated to the incidence of the cancer. Even if the associations suggested by some studies in this body of weak epidemiological evidence are true, the absolute risks for additional cancer cases or deaths are small and cannot necessarily be attributed solely to exposure to SV40-contaminated polio vaccine.

Based on these limitations, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer.**

Biological Mechanisms

Given that the epidemiologic evidence regarding a causal relationship was inconclusive, the committee reviewed the biological evidence with an eye to-

ward additional research that might be needed to better understand the putative role that exposure to SV40 from polio vaccines might have in cancer. The committee reviewed the evidence on biological mechanisms related to this hypothesis through three key questions:

1. Is SV40 a transforming virus?
2. Can SV40 cause cancer in humans under conditions of natural exposure?
3. Is contamination of the polio vaccine with SV40 responsible for SV40 infection in humans?

A wealth of literature exists on topics such as the presence of SV40 in tumors and the effects of the virus or its gene products (particularly Tag, the large tumor antigen) in cell cultures. Several large scientific conferences have also been held to review progress in understanding the role of SV40 in human cancers. Because the Immunization Safety Review Committee was not charged with resolving the full range of uncertainties about the biology of SV40 and the role of this virus in human cancers, the review that follows provides only highlights of the key arguments on these issues. More detailed discussion is available in several excellent and comprehensive reviews (Brown and Lewis, 1998; Butel and Lednicky, 1999; Carbone et al., 1997; Klein et al., 2002; Strickler, 2001b).

Is SV40 a Transforming Virus?

Evidence suggesting that SV40 can produce oncogenic transformation of cells comes from four sources: rodents, nonhuman primates, cell culture studies, and humans.

The earliest studies of SV40 were conducted with rodents and showed that administration to neonatal and weanling hamsters causes cancers. A seminal study (Eddy et al., 1961) demonstrated that injection of extracts of rhesus monkey kidney-cell cultures into newborn hamsters was followed by the occurrence of neoplasms in approximately 70% of the animals. Despite the limitations in their applicability to humans, these animal systems are notable in that the tumors seen—mesothelioma, ependymoma, osteosarcoma, and lymphoma—are the same as the human cancers that have been associated with the presence of SV40 or its Tag or viral fragments in rodents.

Macaques that were immunocompromised as a result of SIV-infection have developed central demyelinating disease (Holmberg et al., 1977; Horvath et al., 1992) suggesting central nervous system (CNS) migration of SV40. At least one SIV-immunocompromised macaque developed an astrocytoma that was positive for SV40 DNA (Hurley et al., 1997).

It was established shortly after the identification of SV40 that the virus can transform cultured human cells (Koprowki et al., 1962). It now appears that the

transforming properties of SV40 are due to the effects of specific gene product, Tag, on key proteins involved in controlling cell growth (Butel and Lednicky, 1999; Kim et al., 1998; Rundell et al., 1998). In particular, Tag inactivates the tumor-suppressor proteins p53 and Rb. These gene products normally suppress tumor growth by preventing cell cycling and by promoting the death of cells with genetic damage. By inactivating these proteins, SV40 Tag promotes both transformation and immortalization of cells. There are an abundance of data from cell culture systems demonstrating effects of SV40 or Tag on many steps related to cell transformation. In addition, evidence from cell cultures of human mesothelial cells suggests that SV40 might preferentially infect these cells without lysis (Bocchetta et al., 2000). This could explain effects of SV40 leading to tumors in some tissues and not others.

Cells transformed by SV40 have been shown to grow in humans and become tumors. In a study by Jensen and colleagues (1964), persons terminally ill with cancer received implants of either homologous or autologous tissue via subcutaneous injection. When cells transformed by SV40 were implanted, nodules of undifferentiated tumor cells developed. This study provides evidence from contrived clinical conditions that cells transformed by SV40 can develop into undifferentiated tumors in a human host.

The committee concludes that the biological evidence is strong that SV40 is a transforming virus.

Can SV40 Cause Cancer in Humans under Conditions of Natural Exposure?

There is a theoretical basis for the existence of mechanisms by which SV40 could cause cancer in humans. The principal lines of evidence for the operation of specific mechanisms are that SV40 acts in ways consistent with tumorigenesis and that DNA sequences consistent with SV40 have been detected in several types of human tumors.

Evidence that SV40 could be tumorigenic comes from *in vitro* studies and studies in animals. These studies, some of which were reviewed above, point to the critical role of SV40 Tag, which is found in the nuclei of transformed cells. As noted, substantial evidence suggests that Tag binds and inactivates the products of tumor-suppressor genes, especially the p53 and Rb proteins. The inactivation of these proteins allows for unregulated cell division (Butel and Lednicky, 1999; Klein et al., 2002).

Data on the association between SV40 and human tumors are inconsistent. A growing body of clinical studies reports the detection of SV40 DNA in several types of tumors. The most notable and well-studied of these is mesothelioma (Carbone et al., 1999). In addition, SV40 DNA has been detected in bone cancers (Carbone et al., 1996), ependymomas (Bergsagel et al., 1992; Lednicky et al., 1995), and in non-Hodgkin's lymphoma (Shivapurkar et al., 2002;

Vilchez et al., 2002). Other studies, however, report an inconsistency or absence of SV40 in mesotheliomas, osteosarcomas, and brain tumors (Engels et al., 2002; Heinsohn et al., 2000; Strickler et al., 1996; Strickler, 2001a).

The conflicting results in the detection of SV40 have also led to questions about technical aspects of the detection of the virus. There are questions as to whether positive findings are the result of overly sensitive but nonspecific tests that are detecting other viruses (i.e., human polyomaviruses BK or JC) or SV40 from laboratory contamination, or whether negative findings arise from a lack of sensitivity in the detection methods used. Two multicenter studies (Strickler, 2001a; Testa et al., 1998) have attempted to resolve some of the uncertainty regarding the detection of SV40 in human mesothelioma samples, but were not successful in resolving the controversy for varying reasons.

The detection of SV40 in tumors does not, by itself, demonstrate a causal relationship. SV40 could be a passenger virus, infecting the cells but causing no pathology. Findings from studies examining SV40 in mesothelioma demonstrate a great deal of variability which precludes the ability at present to draw conclusions regarding the frequency with which SV40 can be detected in specific neoplasms and/or normal tissues in humans. Some studies have detected SV40 in normal tissue from healthy subjects (Martini et al., 1996; Woloschak et al., 1995). Its detection in multiple types of tumors (i.e. its lack of specificity for a single type of cancer) also leads to doubts about a causal link (Strickler, 2001b). **The committee concludes that the biological evidence is moderate that SV40 exposure could lead to cancer in humans under natural conditions.**

Is Contamination of the Polio Vaccine with SV40 Responsible for SV40 Infection in Humans?

Although it is incontrovertible that some polio vaccine was contaminated with SV40, the nature and extent of human exposure to SV40 through this or other sources are less clear. In the United States, potentially contaminated IPV was administered between 1955 and 1963. Because the process for inactivating the live polio virus could be expected to kill some of the SV40, some vaccinees were likely exposed to a mixture of the live and killed virus while others were exposed only to killed SV40. Thus, exposure to IPV between 1955 and 1963 cannot be equated with exposure to live SV40 or, by extension, to infection with SV40.

OPV also was contaminated with SV40. Although the level of contamination was high, exposure was more limited, with approximately 10,000 people who might have received vaccine from contaminated lots (Shah and Nathanson, 1976). Studies showed, however, that the recipients of contaminated OPV produced no antibody response to SV40 (reviewed by Shah and Nathanson, 1976), indicating less likelihood of infection through oral exposure. This suggests that

IPV, not OPV, resulted in the exposure of humans to SV40. Nonetheless, concerns about the validity—and in particular the specificity for SV40—of the serologic testing create some uncertainty about this conclusion.

There is additional uncertainty about the possible contribution of vaccine-based SV40 exposure to SV40 infection and carcinogenesis because of the age at which vaccinees were exposed. Because the incidence of ependymomas is highest in children under age 5 and osteosarcoma is most common in adolescents, contemporary evidence of SV40 in such tumors does not provide a direct link to exposure to contaminated IPV between 1955 and 1963. But with the long latency period for mesothelioma, exposure to contaminated IPV remains a possibility.

Other sources of exposure to SV40 may also exist. A limited number of people are known to have been exposed to SV40 through other vaccines, including an experimental live-virus vaccine against respiratory syncytial virus and a licensed inactivated adenovirus vaccine that was administered to military recruits. Evidence of SV40 exposure has also been detected in serologic samples obtained before 1955 and from studies of persons too young to have received contaminated polio vaccine.

Detection of SV40 in persons too young to have received contaminated polio vaccine suggests the possibility of continuing transmission of SV40 through means other than the polio vaccine. Possible sources of exposure to SV40 are person-to-person transmission, animal-to-person transmission, and laboratory exposure to SV40.

Finally and perhaps most importantly, measures of infection remain problematic. The serology data are unclear, in part because of concerns about cross-reactivity with the JC and BK viruses. The tension between sensitivity and specificity is especially important for this assay because BK and JC are ubiquitous in the human population and SV40 is apparently present only at low levels. **The committee concludes that the biological evidence is moderate that SV40 exposure from the polio vaccine is related to SV40 infection in humans.**

In summary, the committee's scientific assessment concludes that moderate to strong lines of biological evidence support the theory that SV40-contamination of polio vaccine could contribute to human cancers.

Specifically, the evidence is strong that:

- SV40 contaminated some polio vaccine used from 1955-1963, and
- SV40 has transforming properties in several experimental systems.

In addition, evidence has accumulated suggesting that SV40[6] is likely present in some human tumors. The data regarding detection of SV40 in many but

[6] In the form of virus, viral fragments, DNA, or SV40 gene products

not all mesothelioma samples, coupled with the evidence for the oncogenic potential of SV40, suggest that SV40 could contribute to cancers in humans[7]. However, it is not clear

- what proportion (if any) of the people exposed to the SV40-contaminated vaccine were infected,
- what proportion (if any) of the human cancers in which SV40 is detected are caused by the SV40,
- that the sole source of SV40 is due to the contaminated polio vaccine, or
- that SV40-contaminated polio vaccine did or did not cause cancer in the vaccine recipients.

SIGNIFICANCE ASSESSMENT

Most of the issues reviewed by this committee concern vaccines presently in use. In the present case, however, current use of IPV is not in question. The issue instead is the possibility that the occurrence of certain cancers might be related to past use of SV40-contaminated polio vaccine between 1955 and 1963. Even today, this issue carries a major societal significance because exposure to the contaminated vaccine was so extensive and because cancer is such a serious and widely feared disease.

The committee's review of the epidemiologic and biological evidence has shown that the effects of exposure to the contaminated polio vaccine remain uncertain, with important questions regarding the role of SV40 in human cancers unresolved. Even if future epidemiologic studies were to provide more compelling evidence for a causal link, the current evidence is sufficiently robust to suggest that the relative contribution of SV40 to overall risk would have to be small. Nevertheless, the possibility that millions of healthy individuals were exposed to a disease-causing agent could easily damage public confidence in the nation's immunization program and the oversight groups responsible for assuring that it is safe.

The United States has a responsibility to thoroughly address health concerns stemming from the SV40 contamination of polio vaccine to ensure that any adverse health effects are identified and to help produce the scientific evidence necessary for assurance that exposure to the contaminated vaccine has not had adverse effects.

The committee concludes that concerns about exposure to SV40 through inadvertent contamination of polio vaccines are significant because of the seriousness of cancers as the possible adverse health outcomes and

[7] The data regarding mesothelioma are more stubstantial and more abundant than for other cancers, such as non-Hodgkin's lymphoma (NHL), osteosarcoma, or ependymomas.

because of the continuing need to ensure and protect public trust in the nation's immunization program.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

The scientific and policy issues considered by the committee lead to recommendations for targeted public health attention in the form of policy analysis, communication, and targeted research. **The committee does not recommend a policy review of polio vaccine by any of the national or federal vaccine advisory bodies on the basis of concerns about cancer risks that might be associated with exposure to SV40, because the vaccine in current use is free of SV40.**

Policy Analysis and Communication

The committee hopes that contamination of a vaccine never occurs again, but also considers it prudent to have a comprehensive plan in place for prevention of contamination, as well as for response and communication should such an event occur. Pieces of such a plan already exist within the various agencies with responsibility for assuring the safety of vaccines. For example, FDA has regulatory authority over the production of vaccines. Currently, all vaccines licensed by the FDA are required to fulfill general safety, sterility, and purity requirements (Code of Federal Regulations, 2001). However, the committee is not aware of a comprehensive and transparent system. The most recent comprehensive plan by the federal government on vaccine safety does not address contamination issues (NIH, 1998). **The committee recommends that the appropriate federal agencies develop a Vaccine Contamination Prevention and Response Plan.** The appropriate agencies should be given the authority and resources to implement the plan once it is in place. This plan should identify the steps already in place, or those that need to be developed, to prevent contamination of vaccine and to respond to concerns about possible contamination. The plan should include strategies for routine assessment of vaccine for possible contamination; notification of public health officials, health care providers, and the public if contamination occurs; identification of recipients of contaminated vaccine; and surveillance and research to assess health outcomes associated with the contamination. Clearly the plan will need to allow for the scientific and technical uncertainties surrounding an assertion that contamination has occurred or is possible. Implementation of the plan will require considerable judgment as to the level of response required to deal with a specific contamination concern. Because the plan will involve multiple agencies and offices, the National Vaccine Program Office is probably the best positioned to organize and coordinate the development of the plan. Once a plan is developed, a communication cam-

paign should be undertaken to inform the public and medical practitioners. This is important to assure that the trust in the vaccine supply is deserved and is widespread.

Research

The committee recommends development of sensitive and specific serologic tests for SV40. These would be helpful to resolve the question as to whether or not the SV40 exposure led to infection.

The committee recommends the development and use of sensitive and specific standardized techniques for SV40 detection. These efforts should include documentation that: 1) all test specimens are masked, 2) positive and negative control tissues are not only used but subjected to the same processing procedures as test specimens, 3) samples are tested in replicate, and 4) there is an adequate sample of tissue.

The committee recommends that once there is agreement in the scientific community as to the best detection methods and protocols, pre-1955 samples of human tissues should be assayed for the presence or absence of SV40 in rigorous, multicenter studies. This would not address the question of whether or not SV40 can cause cancer, but could influence the interpretation of some epidemiologic and clinical analyses. It would also be relevant for discussion of the relative contribution of contaminated polio vaccine to the SV40 burden of infection in humans.

The committee recommends further study of the transmissibility of SV40 in humans. This will help confirm whether and why SV40 or antibodies specific for SV40 are detected in individuals who have no known exposure to potentially contaminated polio vaccine, animals or laboratory contact. In addition to the research recommended above, it is important to resolve the extent of past SV40 contamination of polio vaccine. The uncertainty of exposure makes interpretation of the epidemiologic studies very problematic. If researchers can pursue these strategies and obtain a better understanding of exposure and methods of detection, more meaningful case-control studies can be undertaken to help resolve the question of causality. **Until some of the technical issues are resolved, the committee does not recommend additional epidemiological studies of people potentially exposed to the contaminated polio vaccine.**

BOX ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer.

Biological Mechanisms Conclusions

The committee concludes that the biological evidence is strong that SV40 is a transforming virus.

The committee concludes that the biological evidence is moderate that SV40 exposure could lead to cancer in humans under natural conditions.

The committee concludes that the biological evidence is moderate that SV40 exposure from the polio vaccine is related to SV40 infection in humans.

SIGNIFICANCE ASSESSMENT

The committee concludes that concerns about exposure to SV40 through inadvertent contamination of polio vaccines are significant because of the seriousness of cancers as the possible adverse health outcomes and because of the continuing need to ensure and protect public trust in the nation's immunization program.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of polio vaccine by any of the national or federal vaccine advisory bodies, on the basis of concerns about cancer risks that might be associated with exposure to SV40, because the vaccine in current use is free of SV40.

Policy Analysis and Communication

The committee recommends that the appropriate federal agencies develop a Vaccine Contamination Prevention and Response Plan.

Research

The committee recommends development of sensitive and specific serologic tests for SV40.

(continued)

Box ES-1 continued

The committee recommends the development and use of sensitive and specific standardized techniques for SV40 detection.

The committee recommends that once there is agreement in the scientific community as to the best detection methods and protocols, pre-1955 samples of human tissues should be assayed for presence or absence of SV40 in rigorous, multi-center studies.

The committee recommends further study of the transmissibility of SV40 in humans.

Until some of the technical issues are resolved, the committee does not recommend additional epidemiological studies of people potentially exposed to the contaminated polio vaccine.

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