Congress did not mandate any specific research, but rather, an extensive review of all the available information on adverse events.

One commenter suggested the IOM incorrectly judged the conclusions of the British National Childhood Encephalopathy Study (NCES). Another commenter stated that the NCES is the only ''suitable'' study that has been done, and that it concluded that there was a causal relationship between the DTP vaccine and permanent neurologic injuries. One commenter also suggested that the NCES proved the onset of a neurologic disorder, including seizures, within 7 days of a DTP vaccination is vaccine-related. The Department has reviewed the conclusions of the NCES in light of these comments, but disagrees for the following reasons.

The 1991 IOM Report considered carefully the results of the NCES, which concluded there is an increased risk of acute neurologic illness (encephalopathy and seizures) within 7 days following DTP immunization, and that in some instances, this may lead to permanent neurologic illness. The methods and results of the NCES have been thoroughly analyzed since publication of the study, which has led to continued controversy about the study's findings and a reassessment of the role of pertussis vaccine as a cause of permanent neurologic damage. (IOM Report, page 99–107)

In its 1991 report, the IOM described potential areas of error and bias regarding the study's conclusions on acute neurologic illness and chronic neurologic damage. Regarding acute neurologic illness, the Committee cited three areas of potential study weakness: case ascertainment, determination of the onset of illness, and the lack of control for potential confounding factors. Despite these limiting factors, the IOM believed that the NCES demonstrated statistical significance for acute neurologic illness where onset is within 7 days of DTP vaccination. Their conclusion was based on the fact that only controlled epidemiological studies can address the relationship between neurologic illness and vaccine causation. Of the four controlled studies reviewed (including the NCES), only the NCES demonstrated a statistically significant risk following DTP vaccine. However, the IOM noted that the ''total number of cases reported in the other three studies was consistent with attributable risk found in the NCES,'' and on this basis concluded *the evidence was consistent* with a causal relation between DTP vaccine and acute encephalopathy. (IOM Report, page 117)

The NCES' conclusion regarding permanent neurologic damage was viewed differently by the 1991 IOM Committee. The Committee described concerns over (1) the number and composition of cases on which the estimates were based and (2) the nature of the relationship between an episode of acute neurologic illness and subsequent demonstration of neurologic or developmental abnormalities. Both concerns cast doubt upon the NCES' conclusion that DTP vaccine causes residual neurologic injury.

The conclusion regarding permanent injury was based on seven children who were found to have residual neurologic illness on follow-up. Since the NCES was published, some of these seven children have been diagnosed with non-vaccine related conditions. Thus, the risk estimates are ''very fragile'' at best, since the number of children with new unexplained neurologic illness was very small. (IOM Report, page 106).

Similarly, the NCES' conclusions on residual effects begs the central question of causation. All seven children found to have ''permanent neurologic illness'' on follow-up were presumed to be normal prior to vaccination. However, no baseline neurologic examination was performed on any of these children. Additionally, two of the seven had seizures as their manifestation of acute neurologic illness within 7 days of DTP vaccination. As the IOM noted, many experts question whether seizures alone cause neurologic illness, or rather are the ''markers'' of those children with pre-existing neurologic disease. (IOM Report, page 107).

As explained above, a follow-up study to the NCES was published by Miller, et al. in the fall of 1993. The Department asked the IOM to look at the Miller study's conclusions regarding DTP vaccine and subsequent neurological damage. The Department then asked a subcommittee of the National Vaccine Advisory Committee (NVAC) to review this later IOM report, as well as the Miller study. The NVAC Subcommittee acknowledged the original NCES (and Miller follow-up) as the most comprehensive long-term study on this subject to date, yet noted there are limitations in the data. These include the lack of neuropathologic studies on case children, the fact that young infants with pre-existing neurologic disorders (damage) can be normal on physical examination at the time of immunization, the failure to exclude alternative etiologic diagnoses, and the non-specific range of disorders classified by NCES authors under the rubric ''chronic nervous system dysfunction.'' The subcommittee noted also that the working definition of ''acute neurologic illness'' used in the NCES is not consistent with the current medical understanding of acute encephalopathy as an acute, generalized disorder of the brain. Children were placed in the NCES case definition who experienced only febrile seizures, a benign condition known to be triggered by DTP vaccine, yet never proven to have lasting effects, absent signs of acute encephalopathy. These limitations disallow definitive causal conclusions that would necessitate changes to the Secretary's definition of encephalopathy in the NPRM.

In reviewing the Miller study, the IOM Committee reached three conclusions:

(a) The evidence is insufficient to indicate whether or not DTP increases the overall risk in children of chronic nervous system dysfunction.

(b) The balance of evidence is consistent with a causal relation between DTP and the forms of chronic nervous system dysfunction described in the NCES in those children who experienced a serious acute neurologic illness within 7 days after vaccine.

(c) The evidence remains insufficient to indicate the presence or absence of a causal relation between DTP and chronic nervous system dysfunction under any other circumstances.

After extensive review and discussion, the NVAC subcommittee agreed with the IOM's conclusion that children who experience serious, acute neurological events after DTP vaccination can go on to exhibit ''chronic nervous system dysfunction.'' The NVAC subcommittee concluded that despite the conclusions of the Miller study, the information remains insufficient to accept or reject whether DTP administration prior to the acute, serious neurologic event influenced the likelihood of neurologic dysfunction. In order to avoid any confusion on this point, the Subcommittee approved the following summary statement:

> Children immunized with whole-cell DTP vaccines rarely experience acute, serious neurologic events that require hospitalization. An important question pertains to the long-term complications of these events. Among all children hospitalized with serious neurologic events, irrespective of their etiology or relationship to DTP, there is a potential for the presence of neurologic dysfunction when they are evaluated 10 years later. However, the data are insufficient to accept or reject whether DTP administration prior to the acute, serious neurologic event influenced the potential for neurologic dysfunction. *See* National Vaccine Advisory Committee (NVAC), Report of the Ad Hoc Subcommittee on Childhood Vaccines, p.7.