EXECUTIVE SUMMARY OF:

"Review of relevant literature on Simian Virus 40 published between July 2000 and November 2002: Update to July 2000 Simian Virus 40 paper presenting recent knowledge on the zoonotic aspects of SV40 and any identified relationship to blood safety"

In July 2000, a paper examining the Rhesus monkey virus, Simian Virus 40 (SV40), and its relationship to polio vaccination in Canada between 1955 and 1962 was prepared for Health Canada. SV40 is a member of the virus family called polyomavirus. This paper examined the published literature to that date examining SV40 and a possible link to the development of certain rare types of cancer. In early 2002, a study providing new information was published in the British journal, "The Lancet". This study indicated that SV40 was found to be associated with a type of cancer called Non Hodgkins Lymphoma (Vilchez RA, et al. 2002). Health Canada determined that an updated review of literature published after July 2000 was needed.

The goal of the literature search was to ensure that documents located would provide published articles and documents which would provide useful and convincing information to help in any future decision making processes. This summary, while not touching upon all aspects of the findings, describes highlights of the results of that search which are of general interest.

SV40 continues to be present in populations world wide at varying incidence rates. Sample sizes, and population groups used in studies to date makes extrapolation to the general population difficult. Regional differences also make conjecture from one part of the world to another difficult, and can affect interpretation of results. In some cases this may be because of limited availability of specimens, territorial differences, or other unknown factors. For example, one of the types of cancer historically associated with the presence of SV40 is malignant pleural mesothelioma (MM). Several studies published during the review period examined the presence of SV40 in MM tumours. In Italy, SV40 was found in 53% of one type of MM examined (Procopio A, et al. 2000), while in Belgium, none of twelve specimens studies indicated presence of SV40 (Hubner et al, 2002).

Today, SV40 is known to be present in children too young to have been exposed to contaminated poliovaccines, although the sources of these SV40 infections are unknown. It is presumed that the virus is being transmitted among humans. Signs of it have been detected in human tumours in a number of studies, including pediatric and adult brain tumours, mesotheliomas (MM), and osteosarcomas (Butel JS. 2000).

Concerns about the possibility of environmental contamination prompted the study of sewage samples from Spain, France, South Africa and Sweden. No SV40 was found in any of the samples examined (Bofill-Mas S, et al. 2000). In a brief report of a presentation made in July 2002, the same group later studied three areas in Northern India. The areas selected were back country monkey habitats, cities with roaming monkeys, and Calcutta, which is outside the monkey's range. All three areas tested positive for SV40. The researchers believe that the high prevalence of SV40 in raw sewage from Calcutta suggests that SV40 is transmitted among

humans (Vastag B. 2002).

The discovery of SV40 in tumours other than malignant mesothelioma has also been explored. For example, the finding of SV40 DNA fragments in tumours prompted a follow-up study on a group of 1073 individuals in the United States known to have received SV40-contaminated polio vaccine. Forty-four deaths had occurred among this group during the period of interest. Of these, four deaths were attributable to cancer. Two deaths from testicular cancer were higher than expected (Carroll-Pankhurst C, et al. 2001). More specifically, ependymal (lining membrane of the brain and spinal cord) tumour samples were studied in Germany. Three of 62 of the tumours exhibited SV40 sequences. Here again, regional differences in exposure to SV40 may explain the relatively low prevalence of tumour associated SV40 sequences found, relative to those found in previous studies done in the USA, Italy and Switzerland (Reuther FJ, et al. 2001).

The non-Hodgkin's lymphoma (cancer of lymphoid tissue) studies (Shivapurkar N, et al. 2002. Vilchez RA, et al. Lancet, 2002) highlight the importance of continued study and examination of other types of cancers with which SV40 may be associated. Non-Hodgkin lymphoma (NHL) is a common malignancy in HIV-infected (AIDS) patients. Samples from both HIV-positive and HIV-negative individuals were tested. SV40 was detected in 23% of the AIDS-related NHL specimens only (Vilchez RA, et al. J Acquir Immune Defic Syndr. 2002). In the Lancet study, Vilchez RA, et al (2002) also examined systemic non-Hodgkin lymphoma (NHL) and non malignant lymphoid specimens from HIV infected and HIV uninfected patients. Colon and breast cancer samples were used as cancer controls. SV40 Tag sequences were found in 64 of 154 non-Hodgkin lymphomas, and that rates were similar for both HIV-positive and HIV-negative patients. None of the other samples showed the presence of SV40. Shivapurkar N, et al (2002) believed that SV40 may be a cofactor in NHL. Their study examined the association of SV40 in non-Hodgkin lymphomas and other human tumours in north Texas, USA. Forty three percent of non-Hodgkin lymphomas were positive for SV40. Three of eight non-Hodgkin lymphoma cases occurred in patients born after 1963, the last known year in which SV40 contamination of polio virus vaccines occurred in the United States.

An antigen is a substance that when introduced into the body stimulates the production of an antibody. One aspect of interest is the antigenicity of SV40. If it is poorly antigenic (unable to stimulate a response), infected individuals may fail to produce detectable levels of antibody. It is also possible that SV40 may be transmitted inefficiently among humans or perhaps only accidental exposures occur (Lednicky JA, et al. 2001). They described the characteristics of "Tag" (large and small "T" antigen of SV40) which may cause normal cells to transform into cancer cells. Expression of Tag, the SV40 oncoprotein, has been observed in some tumours (Butel JS. 2000).

SV40 Tag sequences have been found in 29% of buffy coat of blood samples from blood donors (Martini F et al. 2002). Similarly, neutralizing antibodies to SV40 and SV40 DNA have been found in adult and child kidney transplant patients respectively (Kwak EJ, et al. 2002). SV40 DNA has also been found in the urine, blood and kidneys of adults with focal segmental

glomeruloschlerosis (kidney disease). In addition, SV40 presence in children increased with age and was significantly associated with kidney transplantation. The impact of the presence of SV40 Tag sequences and antibodies in blood and tissue donors is not fully understood.

Several authors described the limitations of currently available diagnostics, including limitations of sensitivity (ability of a test to detect an infection where the infection actually exists), inability to easily distinguish among three polyomaviruses (SV40 and two similar human polyomaviruses), and the potential for confusion with other viral infections (for example cytomegalovirus). The need for the development of specific antiviral therapies is also briefly discussed (Kwak EJ, et al. 2002; Carbone M. 2001; Stratton K, et al.2002). Development of sensitive and specific tests would permit further studies to determine the true prevalence of SV40 infections, and whether SV40 may be transmitted from person to person.

The accuracy of assays performed by nine laboratories was studied by Strickler HD (2001). The investigation was intended to assess the sensitivity, specificity (ability of a test to detect an absence of infection where there is no infection) and reproducibility (how well the test results can be reproduced) of current tests for detection of SV40. Each laboratory was supplied with known positives, known negatives, human mesothelioma samples, and normal human lung. Overall results indicated that most of the SV40 test assays used were sensitive, specific and reproducible, however none of the assays reproducibly demonstrated the presence of SV40 DNA in the human mesothelioma or normal lung specimens. The authors recommend further studies to determine discrepancies between the findings of this study and others.

Limitations continue to exist in the test methods currently in use. A number of the studies and reviews highlight this as a significant problem and suggest the need for improved tests with a reliable sensitivity and specificity. The recommendation by the Institute of Medicine Committee (Stratton K, et al.2002) that additional population studies of people potentially exposed to contaminated polio vaccine not be performed until some of the technical issues are resolved is interesting in view of the suggestion by some of the review papers that further epidemiological studies are needed (Nelson NJ. 2001. Klein G, et al. 2002).

In conclusion, no firm link has established SV40 as a cause of human cancer, although SV40 Tag sequences have been found associated with several tumour types. As in the July 2000 report, more recently published studies continue to show no evidence of a significant increase in rates of cancer. The previous report notes that in hamsters, differences may be seen due to routes of infection, virus dose, age at infection, and influences of other factors including chemical, physical, environmental or other viral elements. The impact of these effects is still not clear in humans.

Continued research into SV40 will continue to be important as SV40 may yet prove to be a cofactor in the development of certain types of cancers.

It is presumed that the virus is being transmitted among humans, but it is not known if this transmission was occurring prior to the use of polio vaccine in the late 1950's and early 1960's,

or was a result of its use. No study has satisfactorily confirmed whether SV40 found in the human population is from contaminated polio vaccine, or from some other source, and epidemiological studies to date have not determined whether SV40-contaminated polio vaccine did or did not cause cancer in the recipients of vaccine.

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