EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C1 - Follow-up and dissemination of scientific opinions

SCIENTIFIC OPINION ON THE USE OF NON-HUMAN PRIMATE MODELS FOR HUMAN TSES ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE AT ITS MEETING OF 6-7 SEPTEMBER 2001

I. OPINION

The Scientific Steering Committee (SSC) was asked whether, in the light of current knowledge concerning the transmission of BSE and vCJD, it considers it justified to perform experiments on non-human primates. If yes, in which context?

In the light of the background report presented in section II, the Scientific Steering Committee considers that studies in non-human primates should make an important and unique contribution to several experiments aimed at quantifying TSE associated risks in humans. They will also contribute important and valuable information to the pre-clinical development of new therapeutic strategies and validation of diagnostic tools. Lemurs, macaques and squirrel monkeys are susceptible to TSE agent infection, and their infection constitutes a valuable scientific and relevant model of human TSEs. In the current stage of the knowledge, apart from future vaccine strategy evaluation, chimpanzees need not to be used in TSE research.

As a general rule, the alleged need for using non-human primates in research projects or testing programmes should be carefully evaluated on a case-by-case basis in the light of this opinion and of existing rules[1] on the use of non-human primates in research and, as far as possible, alternative (including *in vitro*-) models should be used. The SSC recommends that research is done to further identify such alternatives.

Keywords: transmissible spongiform encephalopathy, TSE, primates, testing, research.

II. BACKGROUND REPORT

II.1. Different models can be used to study human TSEs:

- Inoculation of brain or tissue extracts obtained from a patient who died from TSE into mice or guinea pigs or rats. The attack rate of interspecies transmission of sporadic CJD strains to mice is subjected to much variability [1-3]
- Inoculation of mice with British and French vCJD brain extracts results in a high rate of transmission [2-4]

[1] The SSC notes that an ethical review exists as a step in the evaluation process of EU-funded research proposals.

- Inoculation of brain extracts into primates: chimpanzee, macaque, spider monkey and squirrel monkey have been mostly used. Transmission efficacy is above 90 % [5].
- Inoculation of transgenic mice harbouring the human PrP gene: when the genetic background is $PrP^{0/0}$, the rate of transmission is 100 % for all sporadic CJD [6].
- Inoculation of transgenic mice harbouring the bovine PrP gene in a $PrP^{0/0}$ background with vCJD agent results in 100 % transmission [7].

II.2. The applicability of the different models is as follows:

- Transgenic animals (huPrP or BoPrP) are useful for infectivity detection and in some investigations of pathogenesis mechanisms
- Wild type (mice, hamsters, cattle, sheep, minks, goats, cats) and transgenic animals (mainly mice) can be used in basic research at primary passage (pathogenesis, strain typing) and for drug screening once the strains have been adapted (ex: Fukuoka model [8]).
- Non-human primates have a special relevance, as models that can be used for risk assessment in humans: infectious dose by oral route, risk associated with blood, distribution of infectivity during the incubation time. On the other hand, these models are currently irreplaceable for drug and vaccine efficacy[2] and evaluation of diagnostic tools. This is due to the similarity between non human primate and human physiologies: for example, digestive tract, immune system, hematopoïetic system, central nervous systems are similar in humans and in non-human primates. Moreover, most of the biotechnological tools that can be used in humans are applicable to some monkey species; for example, numerous antibodies raised against human CDs are capable to recognise the equivalent surface molecule in macaques. On the other hand, all published data underline the similarity of TSE susceptibililty between monkeys and humans; the level of the species barrier is low.
- One should consider that transgenic animal susceptibility to TSE agents has not been validated against primate models. Some investigations are currently in progress in this field, but it will take years before reliable and complete data are provided (susceptibility may differ depending upon the number of *Prnp* copies in the transgenic animals).

II.3. Use of non-human primates in TSE research.

Due to the Washington convention, and because for certain applications there are alternative models, chimpanzees need, in the current stage of the knowledge not to be used in TSE research apart from future vaccine strategy evaluation.

Apart from chimpanzees, several primate species have been infected with TSE agents (human, bovine, and ovine): macaques and squirrel monkeys are highly susceptible.

[2] Almost certainly, a very important use of non-human primates will be in the realm of therapy. In humans, the 'moment of infection' is unknown (except for the rare instance of iatrogenic disease), and thus prophylactic treatment is not possible. It follows that any drug therapy of humans will not be initiated until symptoms begin, and if the experimental primate model does not have an illness of at least 3-4 weeks, evaluation of the effects of therapy will be difficult if not impossible, given the natural variability in duration of illness in primates, and the fact that no therapy is likely to 'cure' the animal, only prolong the duration of illness. Therefore, it is essential that one or more primate species be chosen that has a comparatively long duration of illness. Available experience with squirrel monkeys indicates that they would probably be a species of choice for at least one species. Further research is needed to confirm this and to identify other species such as, for example, cynomolgus monkeys and microcebes.

These two species can be infected by intracerebral, intraperitoneal and oral routes. There are also strong indications that lemurs are susceptible to CJD, including vCJD and to BSE.

II.4. References:

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