ECETOC Document

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Comments to
Bureau of Chemical Safety
Health Protection Branch
Health and Welfare Dept., Canada
Reproduction Studies

September 1982

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ECETOC

CENTRE D'ECOLOGIE ET DE TOXICOLOGIE
DE L'INDUSTRIE CHIMIQUE EUROPEENNE

EUROPEAN CHEMICAL INDUSTRY ECOLOGY
AND TOXICOLOGY CENTRE

COMMENTS

TO

BUREAU OF CHEMICAL SAFETY

HEALTH PROTECTION BRANCH

HEALTH AND WELFARE DEPT., CANADA

REPRODUCTION STUDIES

Brussels, 7 September 1982.

The Canadian Draft Guidelines require as a minimum a reproduction toxicity study of two generations in rats, with the production of two litters in each generation, the second generation being derived from the second litter of the first generation. Other agencies, notably the EPA and OECD (in its draft) recommend a two-generation study with only one litter per generation.

The Canadian requirement of two litters per generation is based on a review by Clegg (1979) in which, out of 70 multigeneration studies only 4 instances were found of an effect first seen in a second litter, and in each case it was the second litter of the first generation (F_{1b}). In contrast to this, in an extensive review of studies of this type, Palmer (1981) recommends the use of a study design based on the EPA Guidelines with one litter per generation.

ECETOC, having considered these two papers, believes that from a scientific standpoint the multigeneration tests need be performed with only one litter per generation, for the following reasons :

1. The production of a second litter which is also used for deriving subsequent generations is based on historical practice in rodent breeding. Long ago, very young rodents were used to produce offspring, which often showed poor reproductive performance in the first litter. Nowadays, the argument for a larger litter size and a higher viability in the second litter is no longer valid because of the practical experience which has been gained in breeding laboratory rats. In reproduction studies, mating is generally performed only with animals of breeding maturity. In multigeneration studies this is achieved after a pretreatment period of 80 to 100 days. Thus, arguments based on the poor reproductive capacity of animals of the first litter are no longer valid because each pup must be viable, ie. able to reproduce itself regardless of whether it belongs to the 1st, 2nd or last litter. If there is a difference in any parameter between the first and second litter in one generation, the interpretation of this effect can be difficult.

2. Concerning the adverse effects mentioned by Clegg, there is no information about their intensity and significance. In several cases the effects were not dose-dependent. But it is noteworthy that only in 4 out of the 70 three-generation studies evaluated were adverse effects seen in the F_{1b} litter. As this survey shows, in all other cases the adverse effects appeared in the first litter of the first, second or (in one case) of the third generation. But with the exception of aldrin where adverse effects are listed for the F_{1b}, as well as for the F_{2a} and F_{2b} litters, there is no information whether the following litter of the some generation and the litters of the following generation were affected.

3. From his own experience PALMER (1981) concluded that "first matings are as successful and often more successful than second matings in terms of pregnancy rate, litters available at second matings in terms of pregnancy rate, litters available at weaning and litter size. Use of two or more litters per generation more frequently confuses rather than clarifies results, as does routine extension to a third generation".

4. The OECD working group stated that, in the past, the use of 3 or 4 generations and 2 or more litters per generation was preferred because of the limited information on the sensitivity of the test methods. If mature animals are used, and properly maintained, only few differences are expected between the first and second litter. Therefore it was decided not to require any b or c litters for routine investigations.

5. Finally, the duration of exposure to the test substance before mating of the parents is of importance. According to the Proposed EPA Rules, the parental treatment before the first mating should last 100 days. Thus a requirement for two litters per generation means that the second mating would take place at a parental age of 26 to 30 weeks, which is far beyond the time of optimal fertility in rats, even allowing for variation between strains.

The main aim of the reproductive study under consideration is to provide general information concerning the effects of a chemical on reproductive performance and fertility, including gonadal function, oestrous cycles, mating behaviour, conception, parturition, lactation, weaning and the growth and development of the offspring. It is not designed to determine specific causes and effects in all cases. The study may also provide information about the effects of the test compound on neonatal morbidity and mortality, and may give an indication of carcinogenicity or teratogenicity. This information has only an indicative value. A more definite proof of the indicated effects should be obtained from more specific studies such as : certain mutagenicity assays (including "dominant lethal"), teratogenicity testing in rats and rabbits, sub-chronic, chronic and carcinogenicity studies.

To summarise, on the basis of current scientific knowledge a two-generation study with one litter per generation should suffice for the evaluation of the potential reproductive toxic hazard of a chemical. This would have the additional advantage of harmonising the Canadian requirements with those of other authorities.

Bibliography :

- Clegg, D.J. (1979). Animal reproduction and carcinogenicity studies in relation to human safety evaluation. Toxicology and Occupational Medicine - Conference, Miami, 1978. Ed. by W.B. Deichmann, Elseviers North Holland, p.45.

- Palmer, A.K., (1981). Regulatory requirements for reproductive toxicology : theory and practice. Developmental Toxicology. Ed. by C.A. Kimmel and G. Buelke-Sam. Raven Press - New York, p. 259.

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Brussels, 7 September 1982.

Subject : Canadian Draft Guidelines for Pesticide Toxicology Data Requirements.

Gentlemen,

The European Chemical Industry Ecology and Toxicology Centre (ECETOC), an organisation concerned with the scientific aspects of ecology and toxicology, and representing 42 major chemical companies, wishes to comment on some aspects of the above document from the standpoint of a group of its experts in reproductive toxicology. An explanatory Brochure about ECETOC is enclosed.

The Canadian Health Protection Branch of the Health & Welfare Dept. has issued its 6th Draft Guidelines for Pesticide Toxicology Data Requirements, dated 24 July 1981, dealing with Reproduction Studies.

The intention of the Guidelines, which is to assist applicants in selecting the appropriate type of toxicity test essential for the evaluation of pesticide hazards, is fully appreciated. This intention agrees very well with the standpoint of the majority of national regulatory agencies, and also of the chemical industry, both of which are aware of their responsibility in protecting the general population, workers, and bystanders from any health hazards due to the use of chemicals. This aim can be reached satisfactorily only if toxicity testing of a chemical is based on a scientifically-justified programme, which may be drafted in a fruitful dialogue between the applicant and the regulatory agency, instead of following the inflexible requirement of a fixed testing programme.

It also is essential to consider international harmonization with respect to existing guidelines, e.g. the Proposed Rules of EPA/FIFRA which in practice have been the basis for many toxicological investigations during the last few years, and the developing OECD

Guidelines which may well be relevant for future testing. Draft Guidelines for a two-generation reproduction study are still under discussion within the OECD working groups.

We remain,

Very sincerely yours,

L. Turner

L. Turner,
Executive Secretary

cc: SC
Ecetoc Members

Annex : Comments to Bureau of Chemical Safety
Health Protection Branch
Health and Welfare Dept., Canada
Reproduction Studies dated Sept.7, 1982.

Brochure.