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(17) World Health Organization. ''Principles for the Testing and Evaluation of Drugs for Carcinogenicity,'' *WHO Technical Report Series No. 426*. (Geneva: World Health Organization, 1969).

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(19) World Health Organization. ''Part I. Environmental Health Criteria 6,'' *Principles and Methods for Evaluating the Toxicity of Chemicals*. (Geneva: World Health Organization, 1978).

(20) World Health Organization. ''Principles for Pre-Clinical Testing of Drug Safety,'' *WHO Technical Report Series No. 341*. (Geneva: World Health Organization, 1966).

[50 FR 39397, Sept. 27, 1985, as amended at 54 FR 21064, May 16, 1989]

Subpart E—Specific Organ/Tissue Toxicity

§ 798.4100 Dermal sensitization.

(a) *Purpose*. In the assessment and evaluation of the toxic characteristics of a substance, determination of its potential to provoke skin sensitization reactions is important. Information derived from tests for skin sensitization serves to identify the possible hazard to a population repeatedly exposed to a test substance. While the desirability of skin sensitization testing is recognized, there are some real differences of opinion about the best method to use. The test selected should be a reliable screening procedure which should not fail to identify substances with significant allergenic potential, while at the same time avoiding false negative results.

(b) *Definitions*. (1) Skin sensitization (allergic contact dermatitis) is an immunologically mediated cutaneous reaction to a substance. In the human, the responses may be characterized by pruritis, erythema, edema, papules, vesicles, bullae, or a combination of these. In other species the reactions may differ and only erythema and edema may be seen.

(2) Induction period is a period of at least 1 week following a sensitization exposure during which a hypersensitive state is developed.

(3) Induction exposure is an experimental exposure of a subject to a test substance with the intention of inducing a hypersensitive state.

(4) Challenge exposure is an experimental exposure of a previously treated subject to a test substance following an induction period, to determine whether the subject will react in a hypersensitive manner.

(c) *Principle of the test method*. Following initial exposure(s) to a test substance, the animals are subsequently subjected, after a period of not less than 1 week, to a challenge exposure with the test substance to establish whether a hypersensitive state has been induced. Sensitization is determined by examining the reaction to the challenge exposure and comparing this reaction to that of the initial induction exposure.

(d) *Test procedures*. (1) Any of the following seven test methods is considered to be acceptable. It is realized, however, that the methods differ in their probability and degree of reaction to sensitizing substances.

(i) Freund's complete adjuvant test.

(ii) Guinea-pig maximization test.

(iii) Split adjuvant technique.

(iv) Buehler test.

(v) Open epicutaneous test.

(vi) Mauer optimization test.

(vii) Footpad technique in guinea pig.

(2) Removal of hair is by clipping, shaving, or possibly by depilation, depending on the test method used.

(3) *Animal selection*—(i) *Species and strain*. The young adult guinea pig is the preferred species. Commonly used laboratory strains should be employed. If other species are used, the tester should provide justification/reasoning for their selection.

(ii) *Number and sex*. (A) The number and sex of animals used will depend on the method employed.

(B) The females should be nulliparous and nonpregnant.

(4) *Control animals*. (i) Periodic use of a positive control substance with an acceptable level of reliability for the test system selected is recommended;

(ii) Animals may act as their own controls or groups of induced animals can be compared to groups which have received only a challenge exposure.

(5) *Dose levels*. The dose level will depend upon the method selected.

(6) *Observation of animals*. (i) Skin reactions should be graded and recorded after the challenge exposures at the time specified by the methodology selected. This is usually at 24, 48, and 72, hours. Additional notations should be made as necessary to fully describe unusual responses;

(ii) Regardless of method selected, initial and terminal body weights should be recorded.

(7) *Procedures*. The procedures to be used are those described by the methodology chosen.

(e) *Data and reporting*. (1) Data should be summarized in tabular form, showing for each individual animal the skin reaction, results of the induction exposure(s) and the challenge exposure(s) at times indicated by the method chosen. As a minimum, the erythema and edema should be graded and any unusual finding should be recorded.

(2) *Evaluation of the results*. The evaluation of results will provide information on the proportion of each group that became sensitized and the extent (slight, moderate, severe) of the sensitization reaction in each individual animal.

(3) *Test report*. In addition to the reporting requirements as specified under 40 CFR part 792, subpart J, the following specific information should be reported:

(i) A description of the method used and the commonly accepted name.

(ii) Information on the positive control study, including positive control used, method used, and time conducted.

(iii) The number and sex of the test animals.

(iv) Species and strain.

(v) Individual weights of the animals at the start of the test and at the conclusion of the test.

(vi) A brief description of the grading system.

(vii) Each reading made on each individual animal.

(f) *References*. For additional background information on this test guideline the following references should be consulted:

(1) Buehler, E.V. ''Delayed Contact Hypersensitivity in the Guinea Pig,'' *Archives Dermatology*. 91:171 (1965).

(2) Draize, J.H. ''Dermal Toxicity,'' *Food Drug Cosmetic Law Journal*. 10:722–732 (1955).

(3) Klecak, G. ''Identification of Contact Allergens: Predictive Tests in Animals,'' *Advances in Modern Toxicology: Dermatology and Pharmacology*. Ed. F.N. Marzulli and H.I. Maibach. (Washington, D.C.: Hemisphere Publishing Corp., 1977) 4:305–339).

(4) Klecak, G., Geleick, H., Grey, J.R. ''Screening of Fragrance Materials for Allergenicity in the Guinea Pig.–1. Comparison of Four Testing Methods,'' *Journal of the Society of Cosmetic Chemists*. 28:53–64 (1977).

(5) Magnusson, B., Kligman, A.M. ''The Identification of Contact Allergens by Animal Assay,'' The Guinea Pig Maximization Test. *The Journal of Investigative Dermatology*. 52:268–276 (1973).

(6) Maguire, H.C. ''The Bioassay of Contact Allergens in the Guinea Pig'' *Journal of the Society of Cosmetic Chemists*. 24:151–162 (1973).

(7) Maurer, T., Thomann, P., Weirich, E.G., Hess, R. ''The Optimization Test in the Guinea Pig. A Method for the Predictive Evaluation of the Contact Allergenicity of Chemicals,'' *Agents and Actions*. (Basel: Birkhauser Verlag, 1975) Vol. 5/2.

(8) Maurer, T., Thomann, P., Weirich, E.G., Hess, R. ''The Optimization Test in the Guinea Pig: A Method for the Predictive Evaluation of the Contact Allergenicity of Chemicals,'' *International Congress Series Excerpta Medica No. 376*, (1975) Vol. 203.

§ 798.4350 Inhalation developmental toxicity study.

(a) *Purpose*. In the assessment and evaluation of the toxic characteristics of an inhalable material such as a gas, volatile substance, or aerosol/particulate, determination of the potential developmental toxicity is important. The inhalation developmental toxicity study is designed to provide information on the potential hazard to the unborn which may arise from exposure of the mother during pregnancy.