

(c) *Non-positive human studies.* Positive results in human or mammalian studies generally will be used for the qualitative identification of potential occupational carcinogens, even where non-positive results from human studies exist. Such non-positive results will be considered by the Secretary only if the studies or results meet the criteria set forth in § 1990.144(a).

(d) *Non-positive animal studies.* Positive results in one or more mammalian studies will be used for the qualitative identification of potential occupational carcinogens, even where non-positive studies exist in other mammalian species. Where non-positive and positive results exist in studies in the same species, the non-positive results will be evaluated.

(e) *Spontaneous tumors.* Positive results in human or mammalian studies for the induction or acceleration of induction of tumors of a type which occurs "spontaneously" in unexposed individuals will be used for the qualitative identification of potential occupational carcinogens.

(f) *Routes of exposure.* (1) Positive results in studies in which mammals are exposed via the oral, respiratory or dermal routes will be used for the qualitative identification of potential occupational carcinogens, whether tumors are induced at the site of application or distant sites.

(2) Positive results in studies in which mammals are exposed via any route of exposure and in which tumors are induced at sites distant from the site of administration will be used for the qualitative identification of potential occupational carcinogens.

(3)(i) Positive results in mammalian studies in which tumors are induced only at the site of administration, in which a substance or mixture of substances is administered by routes other than oral, respiratory or dermal, will be used as "concordant" evidence that a substance is a potential occupational carcinogen.

(ii) Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in § 1990.144(b) is provided.

(g) *Use of high doses in animal testing.* Positive results for carcinogenicity ob-

tained in mammals exposed to high doses of a substance will be used to establish the qualitative inference of carcinogenic hazard to workers. Arguments that such studies should not be relied upon will be considered only if evidence which meets the criteria set forth in § 1990.144(d) is provided.

(h) *"Threshold" or "No-effect" Levels.* No determination will be made that a "threshold" or "no-effect" level of exposure can be established for a human population exposed to carcinogens in general, or to any specific substance.

(i) *Benign tumors.* Results based on the induction of benign or malignant tumors, or both, will be used to establish a qualitative inference of carcinogenic hazard to workers. Arguments that substances that induce benign tumors do not present a carcinogenic risk to workers will be considered only if evidence that meets the criteria set forth in § 1990.144(e) is provided.

(j) *Statistical evaluation.* Statistical evaluation will be used in the determination of whether results in human, animal or short-term studies provide positive evidence for carcinogenicity, but will not be the exclusive means for such evaluation.

(k) *Carcinogenicity of metabolites.* A substance which is metabolized by mammals to yield one or more potential occupational carcinogens will itself be identified and classified as a potential occupational carcinogen, whether or not there is direct evidence that it induces tumors in humans or experimental animals. Evidence for such metabolism will normally be derived from *in vivo* studies in mammals. In appropriate circumstances, evidence may be derived from *in vitro* studies of mammalian tissues or fractions thereof. Arguments that evidence from *in vivo* metabolic studies in mammals is not relevant to the inference of carcinogenic hazard to humans will be considered only if such evidence meets the criteria set forth in § 1990.144(c).

[45 FR 5282, Jan. 22, 1980; 45 FR 43405, June 27, 1980]

§ 1990.144 Criteria for consideration of arguments on certain issues.

Arguments on the following issues will be considered by the Secretary in

identifying or classifying any substance pursuant to this part, if evidence for the specific substance subject to the rulemaking conforms to the following criteria. Such arguments and evidence will be evaluated based upon scientific and policy judgments.

(a) *Non-positive results obtained in human epidemiologic studies.* Non-positive results obtained in human epidemiologic studies regarding the substance subject to the rulemaking or to a similar or closely related substance will be considered by the Secretary only if they meet the following criteria:

Criteria. (i) The epidemiologic study involved at least 20 years' exposure of a group of subjects to the substance and at least 30 years' observation of the subjects after initial exposure;

(ii) Documented reasons are provided for predicting the site(s) at which the substance would induce cancer if it were carcinogenic in humans; and

(iii) The group of exposed subjects was large enough for an increase in cancer incidence of 50% above that in unexposed controls to have been detected at any of the predicted sites.

Arguments that non-positive results obtained in human epidemiologic studies should be used to establish numerical upper limits on potential risks to humans exposed to specific levels of a substance will be considered only if criteria (i) and (ii) are met and, in addition:

(iv) Specific data on the level of exposure of the group of workers are provided, based either on direct measurements made periodically throughout the period of exposure, or upon other data which provide reliable evidence of the magnitude of exposure.

(b) *Tumors induced at site of administration.* Arguments that tumors at the site of administration should not be considered will be considered only if:

(i) The route of administration is not oral, respiratory or dermal; and

(ii) Evidence is provided which establishes that induction of local tumors is related to the physical configuration or formulation of the material administered (e.g., crystalline form or dimensions of a solid material, or matrix of an impregnated implant) and that tumors are not induced when the same

material is administered in a different configuration or formula.

(c) *Metabolic differences.* Arguments that differences in metabolic profiles can be used to demonstrate that a chemical found positive in an experimental study in a mammalian species would pose no potential carcinogenic risk to exposed workers will be considered by the Secretary only if the evidence presented for the specific substance subject to the rulemaking meets the following criteria:

Criteria. (i) A complete metabolic profile, including identities of trace metabolites, is presented for the experimental animal species;

(ii) A complete metabolic profile, including identities of trace metabolites, is available for a human population group representative of those who are occupationally exposed;

(iii) Documented evidence is provided for ascribing the carcinogenic activity of the substance in the test animal species to metabolite(s) produced only in that species and not in humans; and

(iv) Documented evidence is provided to show that other metabolites produced also in humans have been adequately tested and have not been shown to be carcinogenic.

(d) *Use of high doses in animal testing.* Arguments that positive results obtained in carcinogenesis bioassays with experimental animals subjected to high doses of a substance are not relevant to potential carcinogenic risks to exposed workers will be considered by the Secretary only if the evidence for the specific substance subject to the rulemaking meets the following criteria:

Criteria. (i) Documented evidence is presented to show that the substance in question is metabolized by the experimental animal species exposed at the dose levels used in the bioassay(s) to metabolic products which include one or more that are not produced in the same species at lower doses.

(ii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are the ultimate carcinogen(s) and that the metabolites produced at low doses are not also carcinogenic; and

(iii) Documented evidence is presented to show that the metabolite(s) produced only at high doses in the experimental animal species are not produced in humans exposed to low doses.

(e) *Benign tumors.* The Secretary will consider evidence that the substance subject to the rulemaking proceeding

is capable only of inducing benign tumors in humans or experimental animals provided that the evidence for the specific substance meets the following criteria:

Criteria. (i) Data are available from at least two well-conducted bioassays in each of two species of mammals (or from equivalent evidence in more than two species);

(ii) Each of the bioassays to be considered has been conducted for the full lifetime of the experimental animals;

(iii) The relevant tissue slides are made available to OSHA or its designee and the diagnoses of the tumors as benign are made by at least one qualified pathologist who has personally examined each of the slides and who provides specific diagnostic criteria and descriptions; and

(iv) All of the induced tumors must be shown to belong to a type which is known not to progress to malignancy or to be at a benign stage when observed. In the latter case, data must be presented to show that multiple sections of the affected organ(s) were adequately examined to search for invasion of the tumor cells into adjacent tissue, and that multiple sections of other organs were adequately examined to search for tumor metastases.

(f) *Indirect mechanisms.* The Secretary will consider evidence that positive results obtained in a carcinogenesis bioassay with experimental animals are not relevant to a determination of a carcinogenic risk to exposed workers, if the evidence demonstrates that the mechanism by which the observed tumor incidence is effected is indirect and would not occur if humans were exposed. As examples, evidence will be considered that a substance causes a carcinogenic effect by augmenting caloric intake or that the carcinogenic effect from exposure to a substance is demonstrated to be the result of the presence of a carcinogenic virus and it is demonstrated that, in either case, the effect would not take place in the absence of the particular carcinogenic virus or the augmented caloric intake.

[45 FR 5282, Jan. 22, 1980, as amended at 46 FR 5881, Jan. 21, 1981]

§ 1990.145 Consideration of substantial new issues or substantial new evidence.

(a) *Substantial new issues.* Notwithstanding any other provision of this part, the Secretary will consider in a rulemaking proceeding on a specific

substance any substantial new issues upon which the Secretary did not reach a conclusion in the rulemaking proceeding(s) underlying this part including conclusions presented in the preamble.

(b) *Substantial new evidence.* Notwithstanding any other provision of this part, the Secretary will consider in a rulemaking proceeding on a specific substance any arguments, data or views which he determines are based upon substantial new evidence which may warrant the amendment of one or more provisions of this part. For the purposes of this part, "substantial new evidence" is evidence directly relevant to any provision of this part and is based upon data, views or arguments which differ significantly from those presented in establishing this part, including amendments thereto.

(c) *Petitions for consideration of substantial new evidence—(1) Petition.* Any interested person may file a written petition with the Secretary to consider "substantial new evidence" or one or more "substantial new issues" which contains the information specified in paragraph (c)(2) of this section. The Secretary shall treat such a petition as a request to amend this part, as well as a petition to consider "substantial new evidence".

(2) *Contents.* Each petition for consideration of "substantial new evidence" or one or more "substantial new issues" shall contain at least the following information:

(i) Name and address of the petitioner;

(ii) All of the data, views and arguments that the petitioner would like the Secretary to consider;

(iii) The provision or provisions that petitioner believes are inappropriate or should be added to this part in light of the new data, views, and arguments;

(iv) A statement which demonstrates that the data, views, and arguments relied upon by petitioners are directly relevant to the substance or class of substances that is the subject of a rulemaking or an Advance Notice of Proposed Rulemaking;

(v) A detailed statement and analysis as to why the petitioner believes that the data, views, and arguments presented by the petitioner: