ECETOC Document

No 28

ECETOC Opinion on the SEVESO Directive 82/501, 82/216 and 88/610/EEC Annex II, Part II, Footnote 4 as it Relates to Substances which are not Acutely Toxic but which are Carcinogenic, Mutagenic or Toxic to Reproduction

September 1990

Opinion of the European Chemical Industry Ecology and Toxicology Centre on the SEVESO Directive 82/501, 82/216 and 88/610/EEC Annex II, Part II, Footnote 4 as it Relates to Substances which are not Acutely Toxic but which are Carcinogenic, Mutagenic or Toxic to Reproduction

E C E T O C
Document N°28

September 1990

INTRODUCTION

The 'Seveso Directive' is concerned with "Major Accident Hazards"; for there to be a major accident there should be a "serious danger to man, immediate or delayed, inside or outside the establishment". Immediate effects on health will arise from the acute toxic activity of released substances. Delayed effects will result from acute injury which becomes manifest either shortly after exposure (e.g. pulmonary oedema occurring up to 48 hours after exposure to an irritant gas) or after a longer period (e.g. blindness occurring weeks after exposure, resulting from severe corneal damage caused by caustic gas).

Footnote 4 to Annex II, part II refers to "substances and preparations which, not being acutely toxic, are classified as toxic because of carcinogenicity, mutagenicity or teratogenicity" and includes these in the scope of the directive when they are in a "state which gives them properties capable of causing a major industrial hazard".

Consideration must therefore be given to the state in which substances or preparations capable of causing cancer or mutations or affecting the reproductive processes might, in the absence of acute toxic effects, create a major accident hazard.

This paper considers this issue.

EXPOSURE

For a substance to produce exposure in a large enough number of people for it to constitute a major hazard, it must be readily dispersible. It must, in addition, persist in the environment (air, water or contaminated food), in an absorbable form, long enough to expose body tissues to an amount of substance sufficient to induce a carcinogenic, mutagenic or reprotoxic response. Persistence in body tissues following absorption will increase the possibility that an released substance will produce this sustained tissue exposure.

CARCINOGENICITY

Induction of cancer is a complex process involving a number of consecutive steps (initiation, promotion, progression etc) which occur over a time period which is long compared with the period of exposure likely to occur in a major accident. It is now recognised that a number of substances produce conditions (via cell injury, hormonal action or biochemical changes, for example) which lead to cell proliferation in particular tissues or organs in which cancers eventually develop. With such non-genotoxic carcinogens (e.g. ethanol) prolonged and sustained exposure is required before cancers develop.

Genotoxic carcinogens, i.e. substances that initiate the cancer process by damaging nuclear DNA, also require occurrence of cell proliferation before the altered cells develop into cancers (Ames, 1989*). Thus, again, conditions which give rise to prolonged and sustained cell proliferation are required before cancers develop.

The conditions necessary for the induction of cancers in a population are unlikely to occur in a major accident unless the chemical released persists in the environment to cause prolonged exposure.

Prolonged exposure could arise:

- from ingestion of contaminated water or food;
- from inhalation of gas evolved from contaminated water or soil;
- from skin contact with water, soil or contaminated surfaces.

Recommendation

Materials classified as toxic solely on the grounds of carcinogenicity should be included in the provisions of the directive if they are dispersible and persistent in the environment or they are present in the tissues of exposed persons so that prolonged tissue exposure would occur following emissions.

* Ames B.N., Mutagenesis and Carcinogenesis: Endogenous and Exogenous Factors and molecular Mutagenesis, 14, Suppl 16, 66-77, 1989.

MUTAGENICITY

Damage to nuclear DNA by chemicals has been associated with cancer, reproductive abnormalities, cell death and, in experimental situations, development of heritable disease (anatomical and functional changes). Only heritable disease is considered here. Most mutagenic substances are chemically highly reactive and so are likely to become chemically altered or bound to other materials in the environment before absorption into the body, during absorption or while being transported to the cell nucleus of the germ cells. The fact that no evidence of heritable defects has been discovered in man exposed to chemical mutagens (e.g. anti-cancer drugs) supports this. In addition, there is now ample evidence that everyone is constantly exposed to large quantities of mutagenic substances from food or from natural processes occurring in tissues, and that normally the natural defences of the body prevent heritable changes occurring.

Recommendation

For a mutagen to constitute a major accident hazard it must be dispersible and provide human exposures capable of causing heritable mutagenic changes following a single exposure in animal models.

EFFECTS ON REPRODUCTION

Exposure of experimental animals to some chemical substances has been demonstrated to cause male or female infertility, death of embryos (embryotoxicity) or teratogenic effects (production of young with congenital deformities or permanent functional deficits). Whether such effects occur is strongly dependent on the dose of substance received and, in general, they are not seen in animals unless exposure is high or is persistent over a period of days or weeks. Moreover, there is no evidence of teratogenic effects in man being caused in the workplace by industrial chemicals found to produce terata in experimental animals, and human infertility and death of foetuses have

occurred only following persistent exposure (e.g. to dibromochloropropane) or exposure to substances which accumulate in the body (e.g. lead).

Recommendation

For a substance to constitute a major accident hazard solely because of reprotoxic properties it should be dispersible and in a form capable of producing a short-term exposure or prolonged, lower-level exposure comparable with effective exposures in experimental animals. In practice, the achievement of an exposure sufficient to cause reprotoxic effects is unlikely to occur unless

- reproduction is affected by acute exposure to an unusually small amount of substance;
- reproduction is affected by prolonged exposure to an unusually low concentration of a substance which is persistent in the environment or in tissues.

In both cases such high potency should be readily detected in experimental reprotoxicity studies.

CONCLUSION

The acute toxic properties of a substance will be predominant in determining the danger to man in relation to Major Accident Hazards Legislation. Where there is low acute toxicity, the expression of carcinogenic, mutagenic or reproductive effects justifying classification as 'Toxic' under the Directive would require an unusual combination of dispersibility, persistence in the environment or the human body and high potency in the manner described above. The relative importance and criteria for these characteristics which would lead to a conclusion that the substance is in a form capable of causing a major industrial hazard must remain a matter for professional judgement on a case-by-case basis.