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Chapter 10:

CARCINOGENICITY

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DEFINITIONS

1.   The term "carcinogen" denotes a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

2.   Classification of a chemical as posing a carcinogenic hazard is based on the inherent properties of the substance and does not provide information on the level of the human cancer risk which the use of the chemical may represent.

CONSIDERATIONS

3.   The purpose of the harmonised system for the classification of chemicals which may cause cancer is to provide common ground which could be used internationally for the classification of carcinogenic substances.

4.   The scheme is applicable to the classification of all chemicals. Its application to classification of mixtures is explained in paragraphs 13-18.

CLASSIFICATION CRITERIA FOR SUBSTANCES

5.   For the purpose of classification for carcinogenicity, chemical substances are allocated to one of two classes based on strength of evidence and additional considerations (weight of evidence). In certain instances route specific classification may be warranted.

CATEGORY 1: KNOWN OR PRESUMED HUMAN CARCINOGENS

The placing of a chemical in Category 1 is done on the basis of epidemiological and/or animal data. An individual chemical may be further distinguished:

CATEGORY 1A: KNOWN to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence.

CATEGORY 1B: PRESUMED to have carcinogenic potential for humans; the placing of a chemical is largely based on animal evidence.

Based on strength of evidence together with additional considerations, such evidence may be derived from human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Alternatively, evidence may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

Classification: Category 1 (A and B) Carcinogen

CATEGORY 2: SUSPECTED HUMAN CARCINOGENS

The placing of a chemical in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the chemical in Category 1.

Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Classification: Category 2 Carcinogen

Rationale

6.   **Classification as Carcinogen** is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for chemicals which have an intrinsic property to produce such toxic effects. The evaluations should be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

7.   **Carcinogen classification** is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place chemicals with human cancer potential into hazard classes.

8.   **Strength of evidence** involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms "sufficient" and "limited" are used here

as they have been defined by the International Agency for Research on Cancer (IARC) and are cited in the Background Information for this document.

9. **Additional considerations** (weight of evidence). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

10. The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

11. Some important factors which may be taken into consideration, when assessing the overall level of concern are:

- Tumour type and background incidence.
- Multisite responses.
- Progression of lesions to malignancy.
- Reduced tumour latency.

Additional factors on which the evaluation may increase or decrease the level of concern include:

- Whether responses are in single or both sexes.
- Whether responses are in a single species or several species.
- Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity.
- Routes of exposure.
- Comparison of absorption, distribution, metabolism and excretion between test animals and humans.
- The possibility of a confounding effect of excessive toxicity at test doses.
- Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

12. **Mutagenicity.** It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a chemical has a potential for carcinogenic effects.

CLASSIFICATION CRITERIA FOR MIXTURES

Classification of Mixtures When Data are Available for the Complete Mixture.

13. Classification of mixtures will be based on the available test data of the individual constituents of the mixture using cut-off values/concentration limits for the components of the mixture. The classification may be modified on a case-by case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of carcinogenicity test systems. Adequate documentation supporting the classification should be retained and made available for review upon request.

Classification of Mixtures When Data are not Available for the Complete Mixture.

Bridging Principles

14.   Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, this data will be used in accordance with the following agreed bridging rules. This ensures that the classification process uses the available data to the greatest extent possible in characterising the hazards of the mixture without the necessity for additional testing in animals.

Dilution

15.   If a mixture is diluted with a diluent which is not expected to affect the carcinogenicity of other ingredients, then the new mixture may be classified as equivalent to the original mixture.

Batching

16.   The carcinogenic potential of one production batch of a complex mixture can be assumed to be substantially equivalent to that of another production batch of the same commercial product produced by and under the control of the same manufacture unless there is reason to believe there is significant variation in composition such that the carcinogenic potential of the batch has changed. If the latter occurs, a new classification is necessary.

Substantially similar mixtures

17.   Given the following:

  a).   Two mixtures: i.) A + B
                            ii.) C + B
  b).   The concentration of carcinogen ingredient B is the same in both mixtures.
  c).   The concentration of ingredient A in mixture i equals that of ingredient C in mixture ii.
  d).   Data on toxicity for A and C are available and substantially equivalent, i.e. they are not expected to affect the carcinogenicity of B.

If mixture (i) is already classified by testing, mixture (ii) can be assigned the same category.

Classification of Mixtures When Data are Available for All Components or Only for Some Components of the Mixture.

18.   The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as mentioned in Table 1 below for Category 1 and 2 respectively.

Table 1: Cut-off values/concentration limits of ingredients of a mixture classified as carcinogen that would trigger classification of the mixture[1].

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 carcinogen	**Category 2 carcinogen**
Category 1 carcinogen	≥ 0.1 %	
Category 2 carcinogen	-	≥ 0.1% (note1)
		≥ 1.0% (note 2)

Note 1: If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, every regulatory authority would require information on the MSDS for a product. However, a label warning would be optional. Some authorities will choose to label when the ingredient is present in the mixture between 0.1% and 1%, whereas others would normally not require a label in this case.

Note 2: If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an MSDS and a label would generally be expected.

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[1] This compromise classification scheme involves consideration of differences in hazard communication practices in existing systems. Although it is recognised that this may result in a lack of harmonisation for some mixtures, the OECD Expert Group is recommending to the ILO Hazard Communication Work Group that this compromise be accepted as a way to move the process forward. It is expected that the number of affected mixtures will be small; the differences will be limited to label warnings; and the situation will evolve over time to a more harmonised approach. All of these hazard communication recommendations are subject to review by the ILO Work Group, and may be affected by that group's determinations regarding the possibility of using risk considerations in labelling in the consumer sector.

HAZARD COMMUNICATION

Allocation of Label Elements

19.　　General and specific considerations concerning labelling requirements are provided in Chapter 4. Annex 5 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. Additional reference sources providing advice on the use of precautionary information is also included.
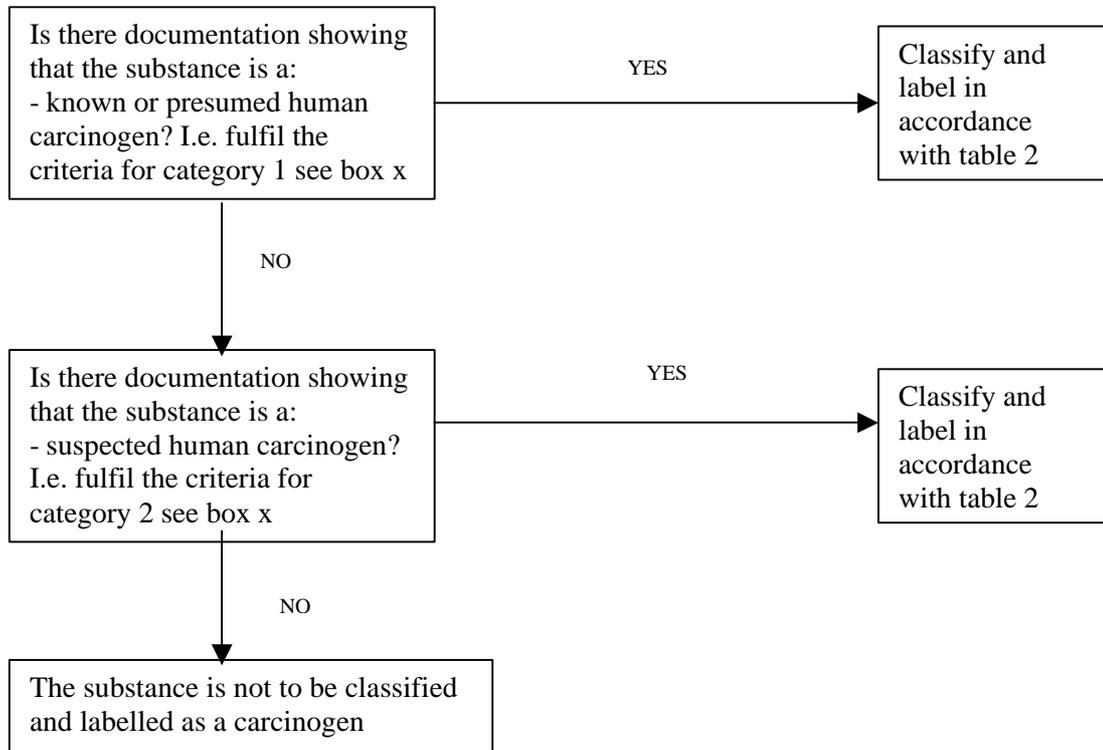
Table 2: Label Elements of Carcinogenicity

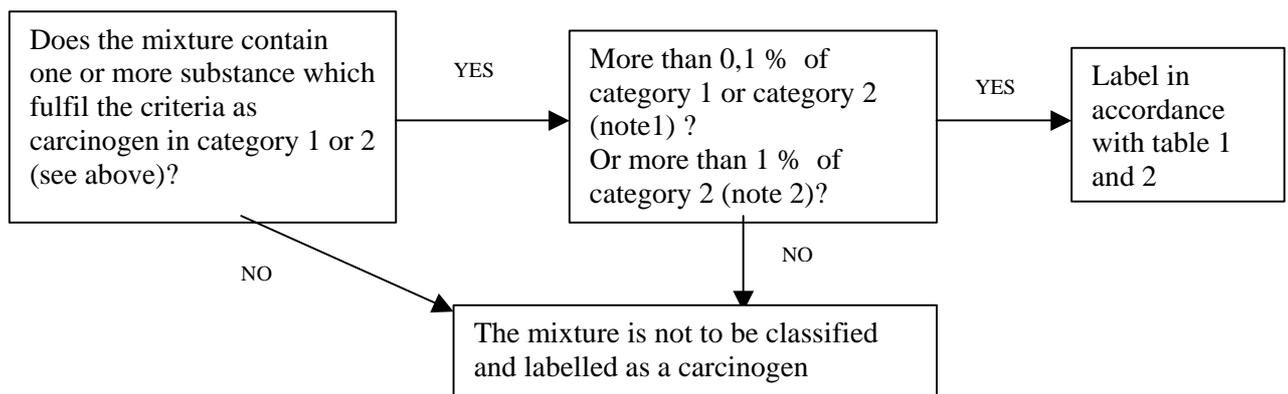|	Category 1A	Category 1B	Category 2
Symbol	New health hazard symbol	New health hazard symbol	New health hazard symbol
Signal Word	Danger	Danger	Warning
Hazard Statement	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

DECISION LOGIC AND GUIDANCE

DECISION TREE FOR CLASSIFICATION AS CARCINOGENS

1. SUBSTANCES

Is there documentation showing that the substance is a: - known or presumed human carcinogen? I.e. fulfil the criteria for category 1 see box x	— YES →	Classify and label in accordance with table 2

NO ↓

Is there documentation showing that the substance is a: - suspected human carcinogen? I.e. fulfil the criteria for category 2 see box x	— YES →	Classify and label in accordance with table 2

NO ↓

The substance is not to be classified and labelled as a carcinogen

2. MIXTURES

Does the mixture contain one or more substance which fulfil the criteria as carcinogen in category 1 or 2 (see above)?	— YES →	More than 0,1 % of category 1 or category 2 (note1) ? Or more than 1 % of category 2 (note 2)?	— YES →	Label in accordance with table 1 and 2

NO (from first box) →
NO (from middle box) ↓

The mixture is not to be classified and labelled as a carcinogen

GUIDANCE

20.   The following additional considerations apply to classification of chemicals into either Category 1 or Category 2. A chemical that has not been tested for carcinogenicity may in certain instances be classified in Category 1 or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

21.   The classification should take into consideration whether or not the chemical is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

22.   It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

23.   It is realised that some regulatory authorities may need flexibility beyond that developed in the hazard classification scheme. For inclusion into Safety Data Sheets positive results in any carcinogenicity study performed according to good scientific principles with statistically significant results may be considered.

24.   Guidance on the importance of the different factors mentioned in paragraph 145 has to be elaborated in order to indicate their effects or level of concern.

25.   The relative hazard potential of a chemical is a function of its intrinsic potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation. Carcinogenic potency as used here does not preclude risk assessment. (See Background Information below).

26.   The proceedings of the recent WHO/IPCS working group to harmonised risk assessment for carcinogenicity points to a number of scientific questions arising for classification of chemicals e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity. Accordingly, there is a need to articulate the principles necessary to resolve these scientific issues which have led to diverging classifications in the past. Once these issues are resolved, there would be a firm foundation for classification of a number of chemical carcinogens.

27.   Data already generated for classifying chemicals under existing systems should be acceptable when reviewing these chemicals with regard to classification under the harmonised system. Further testing should not (normally) be necessary.

Background Information

I.   Evaluation of the Strength of Evidence for Carcinogenicity Arising from Human and Experimental Data Adopted by the International Agency for Research on Cancer (IARC).

Carcinogenicity in humans

28.   The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- **Sufficient evidence of carcinogenicity:** The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed

between exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

- **Limited evidence of carcinogenicity:** A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

29.   In some instances the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

Carcinogenicity in experimental animals

30.   The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- **Sufficient evidence of carcinogenicity:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

- Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

- **Limited evidence of carcinogenicity:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

II.   Considerations of Potency for Labelling Limits

31.   The considerations as laid out below were excerpted from the Report of the Meeting of the Working Group on Harmonisation of Classification and Labelling of Carcinogens, Washington, DC, 17-18 October 1995.

Purpose

32.   The purpose of establishing a potency scheme to be used for labelling of substances, preparations (mixtures) and contaminants is to provide for practical minimum levels of carcinogens in substances for which labelling would be required. It will result in labelling highly potent materials more strictly and less potent materials less strictly. A further purpose is to eliminate unnecessary labelling. In addition, use of a potency scheme may encourage risk reduction through purification of chemical substances or reformulating preparations.

Background

33.   A large number of chemicals have been classified as carcinogenic and placed into various categories for labelling or other regulatory purpose. Chemicals that have been identified as carcinogenic may also occur as components of preparations (mixtures), impurities or additives. Gold and co-authors (Environ Health Perspect 79: 259, 1989) calculated doses from animal testing which result in tumours in half the dosed animals (TD50 values span a range of more than eight orders of

magnitude). Most classification systems do not take into account the wide range of potencies of these chemicals.

34.   Carcinogens are in some countries divided into three potency groups: high, medium and low. Potency is in these instances determined using dose-response data in the observed dosing range for laboratory animals. Additional indicators of potency such as tumour site and species specificity, or species differences in toxicokinetics may also be used. Such potency groups are used to set upper limits for the classification of substances as carcinogens and for the purpose of initiating labelling. They have also been used for the classification and   determination of labelling provisions for preparations (mixtures) of carcinogenic chemicals.

35.   Some countries have implemented a scheme where 0.1% is used as a default limit value for labelling of substances and preparations (mixtures) as carcinogens with sufficient data for carcinogenicity. In these countries chemicals with medium carcinogenic potency are labelled if they occur in chemical substances at or above this level. Many carcinogenic compounds fall into the medium range. Carcinogens with high potency might be classified and labelled at lower levels and carcinogens with low potency could be classified and labelled only when they occur at higher levels. Some countries use 1% as a default limit value for low potency carcinogens and for carcinogens with more limited data.

36.   Some regulatory authorities do not have the obligation to perform potency determinations. If a chemical carcinogen is a candidate for a potency rating outside of the default range, such chemicals should be referred to an international group for its determination.

Observations

37.   The Working Group agreed that it would be useful to explore further the concept of using potency to make labelling decisions. Initial thoughts of the Working Group are presented here.

38.   Potency ranking of carcinogens should not be determined or refined more precisely than by ten-fold factors in light of differences in species response, tumour types and the limits of standardisation of test protocols. In light of these points, a scheme for classification and labelling purposes which separates carcinogens into potency groupings serves the practical purposes listed above.

39.   The use of potency for establishing limits does not preclude the ability of authorities to perform quantitative risk assessments of exposures to carcinogenic substances for regulatory purposes.

40.   Potency determinations should be based on well performed studies which are peer reviewed, performed according to good laboratory practices, or are deemed acceptable by regulatory authorities.

EXAMPLES OF CLASSIFICATION OF SUBSTANCES AS CARCINOGENIC

Illustration 1: Aromatic amine (ARA)

1. STUDIES OF CANCER IN HUMANS

Cohort study

A cohort of 587 male workers was set up at a plant manufacturing ARA including all employees working in 1980 at the time when the cohort was established and all past employees in the manufacturing process since 1965. The mortality was assessed up to the end of 1990. 2.5% of the cohort could not be traced. Reference rates from the countries were obtained. Overall, 63 deaths occurred versus 69.5 expected (standard mortality ratio [SMR], 0.9 [95% confidence interval (CI), 0.8-1.0]) including 25 cancer deaths versus 22.2 expected (SMR, 1.1 [95% CI, 0.7-1.5]). When a 10-year latency was imposed between the start of exposure and start of follow up, an excess of mortality from bladder cancer was observed (SMR, 2.3 [95% CI, 0.8-4.2]), increasing to 3.3 after 15 years. Additional analysis by job and categories of exposure to chemicals did not identify any risk factor for bladder cancer. An examination of the exposure level and time since exposure of the bladder cancer did not support a causal interpretation.

2. STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

2.1 Oral administration

2.1.1 Mice

Groups of 50 male and 50 female B6C3F1 mice, six weeks of age, were administered ARA (purity, >99%) in the diet at 0, 1500 or 3000 ppm for 102-103 weeks. Mean body weights of both treated males and females were lower than those of the corresponding controls. Mortality was not significantly related to treatment in either sex. In male mice, the incidence of haemangiomas or haemangiosarcomas (combined, all sites, mainly observed in the abdominal viscera) was increased: 2/49 (4%), 4/50 (8%) and 12/50 (24%) ($p<0.002$, Cochran-Armitage trend test) in control, low-dose and high-dose groups, respectively. In female mice, the incidence of hepatocellular adenomas or carcinomas (combined) was increased: 0/50 (0%), 4/49 (8%) and 13/50 (26%; $p<0.007$, Fisher's exact test; $p = 0.001$ trend test) in control, low-dose and high-dose groups, respectively (1).

2.1.2 Rats

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were administered ARA (purity, >99%) in the diet at concentrations of 0, 2000 or 4000 ppm for 102-103 weeks. Mean body weights of treated male and female rats were lower than those of the corresponding controls. Mortality was not significantly affected by the treatment. In male, the incidence of sarcomas, fibrosarcomas, angiosarcomas or osteosarcomas (combined) of multiple organs was 0/50 (0%), 15/50 (30%; $p = 0.003$, Fisher's exact test) and 40/50 (80%; $p>0.001$); and that of mesotheliomas of multiple organs or tunica vaginalis was 0/50 (0%), 18/50 ($p<0.001$, Fisher's exact test) and 22/50 (44%; $p<0.001$) in control, low- and high-dose groups, respectively. In females, the incidence of transitional cell carcinomas of the urinary bladder was 0/50 (0%), 9/45 (20%; $p = 0.03$) and 25/50 (50%; $p<0.001$); that of sarcomas, fibrosarcomas, osteosarcomas or angiosarcomas (combined) of multiple organs was 0/50 (0%), 5/50 (10%) and 22/50 (44%; $p = 0.001$) (2).

3. OTHER DATA RELEVANT TO ITS EVALUATION OF CARCINOGENI-CITY AND ITS MECHANISMS

3.1 Genetic and related effects

3.1.1 Humans

No data available

3.1.2 Experimental systems

See evaluation of mutagenicity. Bacterial assay system showed negative or at most weakly positive results. In cultured mammalian cells, ARA caused sister-chromatid exchanges and some times also increased gene mutation, chromosomal aberration and micronuclei. The substance induced anaploidy and increased cell transformation in mammalian cells. In rodent models *in vivo*, it enhanced sister-chromatid exchange and micronuclei formation.

4. EVALUATION

Only one epidemiological study was available for evaluation. In cohort study in a factory producing ARA, an increase in bladder cancer was observed. However, an examination of the exposure levels and time since exposure of the bladder cancer cases did not support a causal interpretation. The study provides inadequate evidence in humans for carcinogenicity.

ARA was tested for carcinogenicity in one experiment in mice and one in rats. After oral administration to mice, it induced haemangiomas and haemangiosarcomas and hepatocellular carcinomas or adenomas. In rats, it increased the incidence of tumours in multiple organs, including sarcomas, mesotheliomas and transitional-cell carcinomas of the urinary bladder. The two studies provide sufficient evidence for carcinogenicity in experimental animals.

Studies on genotoxicity and mutagenicity demonstrated mutagen effects in mammalian cells *in vitro* as well as formation of sister chromatid exchanges and micronuclei *in vivo* in rodents. The studies provide evidence that genotoxic mechanisms may be involved in the induction of tumours.

5. OVERALL EVALUATION

Alternative 1:

a) There is *inadequate* evidence in humans for carcinogenicity of ARA.

b) There is *sufficient* evidence in experimental animals for the carcinogenicity of ARA.

c) There is evidence that the induction of tumours involve a genotoxic mechanism.

ARA is presumed to have carcinogenic potential for humans; the placing of the chemical is largely based on animal evidence (category 1B).

Alternative 2:
While there is inadequate evidence in humans, there is sufficient evidence in experimental animals and therefore ARA is presumed to have carcinogenic potential for humans, placing it in category 1B.

6. REFERENCES

Illustration 2; Cyclic aromatic compound (CAC)

1.   STUDIES OF CANCER IN HUMANS

Cohort study

A cohort of 743 male workers was set up in a plant using CAC in the production of a pesticide. The workers had been employed at least 5 years on 1 August 1965. Follow-up covered a period from 1 January 1965 through 1975. Overall, 75 deaths were observed versus 96.3 expected. Standard mortality ratio [SMR], 0.8 [95% confidence interval (CI), 0.6-1.0]), including 29 cancer deaths versus 27. expected (SMR, 1.1 [95% CI, 0.7-1.5]). When a 10-year latency was imposed between the start of exposure and the start of follow-up, an excess mortality from lung cancer was observed (SMR=2.5 [95% CI, 0.9-3.8]), increasing to 3.5 after 15 years. No correction has been made for smoking (1).

2.   STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

2.1   Oral administration

2.1.1 Mice

Groups of 50 male and 50 female B6C3F1 mice, six weeks of age, were exposed to CAC in the diet at concentrations of 0, 500 or 1.000 ppm. Mean body weight of the exposed animals were reduced at the high dose. Survival was not influenced by the treatment. Hepatocellular adenomas occurred at an increased incidence in males: 29/50 (58%), 41/50 (82%; p= 0.03 Fisher's exact test), 40/50 (p = 0.03) in control, low- and high-dose mice, respectively. The incidence of hepatocellular carcinomas in males was: 15/50 (30%) control, 35/50 (70%; p<0.001) low-dose and 41/50 (82% p<0.001) high-dose mice, respectively. In female mice, the incidence of hepatocellular carcinomas was increased in a dose-related manner: 13/49 (27%) control, 23/50 (46%) low-dose and 41/50 (82%; p<0.001) high-dose mice (2).

2.1.2 Rats

Groups of 50 male and 50 female Fisher 344/N rats, eight weeks of age, were given drinking-water containing 0, 200 or 400 ppm for 103 weeks. The treatment did not

influence the weight of animas nor the survival. No significant increase in tumour frequency was observed (3).

3. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISM

3.1 Genetic and related effects

3.1.1 Humans

No data available.

3.1.2 Experimental systems

Apart from positive responses in the sex-links recessive lethal assay in *Drosophila melanogaster* and for anaploidy in a fungal system, all tests, covering a range of end-points for genotoxicity of CAC in bacteria as well as mammalian cell *in vitro* gave negative results.

4. EVALUATION

Only one epidemiological study was available for evaluation. In a cohort study in a factory using CAC, an increase in lung lancer was observed. However, no correction for smoking had been carried out. The study provides inadequate evidence in humans for carcinogenicity.

CAC was tested for carcinogenicity in one experiment in mice and one in rats. After oral administration to mice, it induced hepatocellular adenomas and carcinomas in both sexes. In rats, no tumours were observed. However, the concentrations used could probably been higher. The two studies provide limited evidence for carcinogenicity in experimental animals.

Study on genotoxicity gave little evidence for induction of tumours by a genotoxic mechanism. However, more studies may be required before a genotoxic mechanism can be completely ruled out. The studies provide little or no evidence that genotoxic mechanisms may be involved in the induction of tumours.

5. OVERALL EVALUATION
Alternative 1:

a) There is *inadequate* evidence in humans for the carcinogenicity of CAC.

b) There is *limited* evidence in experimental animals for the carcinogenicity of CAC.

c) There is little or no evidence that the induction of tumours involve a genotoxic mechanism.

CAC is a suspected human carcinogen; the classification of the chemical is mainly based on limited animal evidence (category 2).

Alternative 2:
While there is inadequate evidence in humans, there is limited evidence in experimental animals and little or no evidence for genotoxicity; therefore CAC is presumed to be a suspected human carcinogen, placing it in category 2.

6.   REFERENCES

Illustration 3; Organic peroxisome proliferator (OPP)

1.   Studies of cancer in humans

No data available.

2.   Studies of cancer in experimental animals

2.1 Oral administration

2.1.1 Mice

Groups of 50 male and 50 female B6C3F1 mice, six weeks of age, were fed diet containing 0, 10.000 or 20.000 ppm OPP for 103 weeks and were killed 104 weeks after the beginning of treatment. Mean body weight of treated mice of each group was lower than those of the corresponding control and the decrease in weight gain was dose related. The survival of the treated animals were similar to that of the controls. OPP increased the incidence of hepatocellular adenomas in both males (4/50 (8%) control, 8/50 (16%) low-dose and 15/50 (30%; $p < 0.0025$ Fisher's exact test) high-dose animals and females (1/50 (2%) control, 4/50 (8%) low-dose, and 6/50 (12%) high-dose animals). Hepatocellular carcinomas were observed in 6/50 (12%) control, 10/49 (20%) low-dose, and 13/49 (27%) high-dose males and 1/50 (2%) control, 14/50 (28%; $p < 0.001$) low-dose, and 20/50 (40%; $p < 0.001$) high-dose females. The incidence of hepatocellular adenomas and carcinomas combined were significantly increased both in males and females (1).

2.1.2 Rat

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were fed diet containing 0, 10.000 or 20.000 ppm OPP for 103 weeks and were killed 105 weeks after the beginning of treatment. Mean body weight of high-dose rats of each group was lower than those of the corresponding controls. The survival of the treated animals were not influenced by the treatment. High-dose male rats had a significant increase ($p = 0.01$, Fisher's exact test) in the combined incidence of hepatocellular carcinomas and neoplastic nodules (control, 2/50 (4%); low-dose, 5/50 (10%); high-dose 13/50 (26%)) (The term neoplastic nodule is now generally assumed to represent hepatocellular adenomas). The incidence of hepatocellular carcinomas alone or neoplastic nodules alone was not significantly increased. In female rats, the incidence of hepatocellular carcinomas was increased in high dose rats (8/50; 16%; $p = 0.003$) compared to controls (0/50; 0%) and that of neoplastic nodules was also increased in high dose females (6/50 12%; $p < 0.03$ compared with controls (0/50; 0%). The incidence of hepatocellular carcinomas and neoplastic nodules combined was also increased in low-dose (8/50; 16%; $p < 0.01$), and high-dose (15/50; 30% ; $p < 0.001$) females compared with controls (0/50; 0%) (2)

3. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISMS

3.1 Toxic effect

A considerably amount of information on the hepatic effect of orally administered OPP indicate that it causes peroxisome proliferation (ultrastructural effects and enzyme induction), hepatomegaly and increased replicative DNA synthesis in rats and mice. Hepatic peroxisome proliferation depends on a nuclear receptor, PPARα, to mediate these effects in mice, based on lack of response to peroxisome proliferators in PPARα-deficient mice. Oral administration of OPP failed to elicit markers of peroxisome proliferation in PPARα-deficient mice, while the same treatment elicited this response in normal mice.

3.2 Genetics and related effects

3.2.1 Humans

No data available.

3.2.2 Experimental systems

OPP has been studied extensively for its genotoxic effects in a wide range of test systems, both *in vitro* and *in vivo*. The majority of these studies did not reveal any activity. No mutagenic activity was observed in bacteria. In fungi, there was no evidence of recombinational events or mutation. In cultured mammalian cells, no primary DNA damage, mutation, sister chromatid exchange or chromosomal aberrations were induced. *In vivo*, neither covalent binding to DNA nor DNA strand breakage was induced. Dominant lethal effects were not found in male mice.

4. EVALUATION

No epidemiological studies in relation to exposure to OPP has been found.

OPP was tested for carcinogenicity in one experiment in mice and one in rats. After oral administration to mice it induced hepatocellular adenomas and carcinomas in both males and females. In rats, it increased the incidence of neoplastic nodules in the liver and of hepatocellular carcinomas in both sexes. The two studies provide sufficient evidence for carcinogenicity in experimental animals.

OPP did not demonstrate any genotoxic activity.

Studies of hepatic peroxisome proliferation in rats and mice demonstrated that OPP caused peroxisome proliferation both in mice and rats. The data provide evidence that the tumour formation in mice and rats are induced by a mechanism involving peroxisome proliferation.

5. OVERALL EVALUATION
Alternative 1:
a) There is *inadequate* evidence (no data) in humans for the carcinogenicity of OPP.

b) There is *sufficient* evidence in experimental animals for the carcinogenicity of OPP.

c) There is no evidence that the induction of tumours involve a genotoxic mechanism.

d) There is evidence that the induction of tumours involve peroxisome proliferation.

In making the overall evaluation of the carcinogenicity to humans of OPP, it is taken into consideration that (i) OPP produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (ii) peroxisome proliferation has been demonstrated under the conditions of the carcinogenicity studies of OPP in rats and mice; and (iii) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to OPP nor in the liver of exposed non-human primates. Therefore, the mechanism by which OPP increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.

OPP is not presumed to have carcinogenic potential for humans (no classification).

Alternative 2:
In making the overall evaluation of the carcinogenicity to humans of OPP, it is taken into consideration that (i) OPP produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (ii) peroxisome proliferation has been demonstrated under the conditions of the carcinogenicity studies of OPP in rats and mice; and (iii) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to OPP nor in the liver of exposed non-human primates. Therefore, the mechanism by which OPP increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.

While there are no studies in humans, there is sufficient evidence for carcinogenicity in experimental animals. However the mechanism of tumour formation in animals is not considered relevant for humans, hence OPP is not presumed to have carcinogenic potential for humans, no classification.

6. REFERENCES