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OPINION OF THE SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE) ON

"ASSESSMENT OF THE EUROPEAN COMMITTEE FOR STANDARDISATION (CEN) REPORT ON THE RISK ASSESSMENT OF ORGANIC CHEMICALS IN TOYS"

REPORT VERSION:
Final Report of the work of CEN/TC 52/WG 9 - January 2003
(Contract BC/CEN/97/29.1.1)

Adopted by the CSTEE during the 40th plenary meeting on 12 November 2003

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BACKGROUND

Council Directive 88/378/EEC of 3 May 1988 on the Safety of Toys, amended by Council Directive 93/68/EEC of 22 July 1993, lays down essential safety requirements that toys must fulfil before being placed on the market. The Directive (Annex II, II, 3) states that toys must be so designed and constructed that, when used as intended or in a foreseeable way bearing in mind the normal behaviour of children, they do not present health hazards or risks of physical injury by ingestion, inhalation or contact with the skin, mucuous tissues or eyes. The Directive also requires that "toys must not contain dangerous substances or preparations within the meaning of Directives 67/548/EEC on the classification, packaging and labelling of dangerous substances and 88/379/EEC in amounts that may harm the health of children using them."

In 1992, the Toxicology Section of the Scientific Advisory Committee examining Toxicity and Ecotoxicity was consulted and issued an opinion relating to the toxicity of certain organic compounds in toys (EUR 13976, 1992).

Further to this opinion, the Commission gave mandate to the European Committee for Standardisation (CEN) on "organic chemical compounds in toys other than chemical toys" in 1996 for the preparation of European standards concerning the risks associated with the presence of organic chemical compounds in toys.

In accordance with the contract BC/CEN/ENTR/229/97-29-Amendment 1 July 2002, CEN has been asked to prepare three following European standards:

- pr EN 71-9:2002 "Safety of toys – Part 9: Organic chemical compounds – Requirements". This standard must specify requirements for the migration or content of certain hazardous compounds from toys and toy materials.

- pr EN 71-10:2002 "Safety of toys – Part 10: Organic chemical compounds – Sample preparation and extraction procedures". This standard must specify sample preparations and extraction procedures for establishing the release or content of organic compounds from those toys for which requirements were established in the previous draft standard.

– pr EN 71-11 “Safety of toys – Part 11: Organic chemical compounds – Methods of analysis”. This standard must specify methods for the analysis of toys and toy materials extracts prepared according to the procedures established in pr EN 71-10: Part 10: – “Sample preparation and extraction procedures” and to enable compliance with the chemical requirements specified in pr EN 71-9:2002 Part 9: “Requirements” to be assessed.

CEN was also asked to provide two Reports on “Risk Assessment” and “Methods of Analysis” as a support to the development of the three European standards above mentioned. The first report “Risk assessment” and the two related draft standards pr EN 71-9:2002 “Safety of toys – Part 9” and pr EN 71-10:2002 “Safety of toys – Part 10” were submitted to the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) together with the following request:

Terms of Reference

(1) The SCTEE is requested to assess the overall scientific quality of the CEN risk assessment report and the resulting draft standards. In considering this, the committee is asked to comment on the overall approach and methodology, the assumptions used, the analyses carried out and the conclusions of the risk assessment report.

(2) If the CSTEE disagrees with the overall approach or any assumptions, reasoning or conclusions of the risk assessment report, the CSTEE is invited to elaborate on the reasons for this divergence of opinion and to make suggestions on how to improve the risk assessment of the organic compounds considered in the CEN report.

CONCLUSIONS

1) The report focuses on hazards not risks

The report does not cover exposure assessment and rather concerns hazard identification and not risk assessment. Consequently the title is misleading since only hazards are addressed.

2) There is confusion between risk assessment and risk management

The general impression of the present report on the risk assessment of exposure to organic chemicals in toys is disturbed by not making a clearer distinction between risk assessment and risk management issues. Also, the report is clearly deficient with respect to its use of proper risk assessment terminology, such as using the word "risk" when it should have been "hazard".

3) The report does not follow the ECB approach

The overall scientific quality of the risk assessment report is poor as i) its description of basic toxicological principles, such as oral, inhalation and dermal absorption processes is rather poor, ii) in the toxicological evaluation the ECB database on existing chemicals is not used.

4) Basis for selecting chemicals

The sequence of events which led to the formulation of the Report, and are reflected in its different Sections, is unclear. It appears that initially (end of 1998) a list of more than 650 chemicals of potential significance regarding toys was drawn up (Annex C, page 111), from which an "initial priority list" of approx. 380 chemicals was selected (Annex E, page 145), with criteria which are not stated. Following clarification from the Commission (December 2001) that only substances officially classified under Dir. 67/548 were to be investigated, 75 chemicals were further identified as "First Priority" (Annex F, page 165).

There is a lack of clarity in the Report as to why some chemicals are excluded. This should have been explained. For example, it is noted that 5 of the 58 preservatives listed in Table 1 are not mentioned in Tables 2-4 (compounds 22, 23, 27, 32, 33). Some phthalates known to be used in toys (currently or in the past) were not evaluated (e.g. DINP, DEHP and DIDP). In the summary (page ix) this is mentioned but not justified. No consideration is given to organotin compounds.

5) Deficiencies in presentation of the outcome of the implementation of the Ranking system

One hundred and eighty-three chemicals (from the "initial priority list") appear to have been evaluated and their evaluations form the basis of the Position Paper describing the ranking scheme (Annex D, page 137). However, some of the numbers of evaluated chemicals given in Annex D differ from those mentioned in the main Report, causing confusion: for example, in Annex D it is indicated (page 139) that 48 flame retardants were evaluated, of which 19 were ranked at 9 or 10. On the other hand, on pages 34-35 it is said that 11 out of 43 flame retardants were ranked at this level. Similar contradictions are found in other places. Furthermore the ranking scheme used in the report is not applied to all groups of chemicals.

6) Utility of the report

There are numerous inconsistencies and errors in the report. In addition the report is not useful for the initial purpose; it does not provide a suitable basis for setting standards. The CSTEE does not recommend its use for risk prioritisation purposes in its present form.

DETAILED COMMENTS

Chapter 1. Introduction

1.2. Work programme

It should be pointed out that the substance categorisation used is not solely based on risk assessment but may include risk management decisions such as the use of the precautionary principle (page 3, bottom paragraph).
The CSTEE recommends that a clear distinction is made between risk assessment and risk management factors in determining substance categorisation.

Chapter 2. Assessment of the health risks of chemicals

The chapter correctly describes the commonly used approaches in the risk assessment process in identifying the intrinsic toxic properties of a chemical by identification of the relevant endpoints, the dose response of the critical effects, NOAEL in case of thresholded effects and in case of carcinogens differentiation between genotoxic and non-genotoxic mechanisms.

However, the need to understand the underlying mechanisms of the toxic effects to differentiate between thresholded and non-thresholded mechanisms and to extrapolate from animal studies to man has not been properly addressed.

Reference should be given to the use of other surrogates of the dose threshold than the NOAEL, such as the benchmark dose, that may be used (page 6, third paragraph and throughout).

The report suggests that except for pesticides little information on toxicokinetics is usually available for existing chemicals. When adequate human data are available, they are applicable to identify hazards to humans and can directly be used to define upper limits for the estimated dose of concern. This has not been done properly in the report.

2.5. Toxicity data for animal studies

2.5.2. Skin and eye irritancy and skin sensitisation

Mention of respiratory sensitisation as an important endpoint should have been given (page 8).

2.5.4. Mutagenicity

The term "*in vitro*" should be "*in vivo*" (page 8, second paragraph, fifth line).

The bone marrow micronucleus assay is also a main somatic cell assay for clastogenicity (page 9, first paragraph).

2.5.5. Carcinogenicity

The CSTEE agrees that there normally will not be a need for a carcinogenicity bioassay for a non-genotoxic chemical, if the exposure was chiefly from toys.

2.5.6. Reproductive toxicity

The tests for reproductive toxicity also include tests for postnatal developmental effects (page 9, first paragraph).

2.5.7. Toxicokinetics

Comparative metabolism information may be available from *in vitro* systems (page 9).

2.6. Exposure assessment

Exposure assessment indicates the need to use measured data or data from exposure modelling and lists default parameters for calculation of limits for different products as well as amounts of toy material that could be consumed a day (solids 1g, liquids 25ml, play clays 10g). The scientific rational for these figures is not fully justified in the report.

The CSTEE agrees with the general approach for the identification of NOAELs, evaluation of non-thresholded carcinogens and risk assessment and derivation of "Acceptable/Tolerable Daily Intakes". Unfortunately this approach was not followed consistently in practise.

2.6.1. Exposure risk assessment by computer modelling

Reference should have been given to the nature of the sub-population groups exposed, in particular children.

Here a breathing rate for children is given as 10 litres per minute, which equates to 0.6 m^3 per hour (14.4 m^3/day). In the table on page 21, ventilation rates are presented to vary from 0.08 to 0.292 m^3/hour (2.0-7.0 m^3/day). The default parameter on page 11 must presumably relate to adults, and thus is not appropriate (page 11, Default parameters, breathing rate).

2.7. Risk characterisation

2.7.1. Identification of critical effect and NOAEL

The use of a NOAEL derived from a 28-day study is not a reliable basis for evaluating systemic effects and is not part of normal practise (page 12, second paragraph).

The term "subacute" should be deleted from the report (page 12, second paragraph).

2.7.2. Integration of exposure and effect to characterise risk

The relevance of the underlying mechanisms for the toxic effects for humans should have been mentioned (page 12, listing of factors at the bottom of the page).

Other relevant factors which have not been considered are: differences in exposure duration (and frequency and pattern), differences in route of exposure, and dose-response relationship.

As to adequacy and confidence in the database, the CSTEE notes that the database should contain sufficient information on the effects of a substance on the developing organ systems and functions, especially since exposure from toys is specific for (young) children.

2.7.3. Assessment factors

The use of an additional assessment factor for nature of toxicity is a risk management decision, not a risk assessment issue (page 13 and figure on page 14).

2.8. Outcome of risk assessment

2.8.1. Route of exposure and route-to-route extrapolation

It should have been explained in the report that route-to-route extrapolation in general is a poor substitute for data obtained using the appropriate route, and can only be applied if certain criteria are met. It requires careful consideration of the nature of the effect and of the toxicokinetic data.

There is no stated scientific basis for the extrapolation used in the report.

The source of the assessment factors is not given in the section 2.7.3. The rationale for using them is not justified.

2.8.2. Estimation of approximate dermal NOAEL from oral NOAEL

The CSTEE notes that in the revised TGD for new and existing substances in the absence of substance-specific absorption data, a default factor of 2 is currently being proposed, resulting in a 2-fold lower dermal or inhalation NOAEL (end route) than the oral NOAEL (starting route). NB: the default for absorption by inhalation should be generally 100% (or sometimes 75%), but not 50% as used in the report (stated on page 15). 100% is also mentioned in the summary on page iv but not subsequently used.

The CSTEE notes that default factors are addressed in the revised TGD.

2.8.3. Estimation of approximate inhalation NOAEL for oral NOAEL

The CSTEE disagrees with the use of acute inhalation toxicity data to derive an inhalation NOAEL. Also particles between 5 μm and 10 μm are respirable (not "respiritable").

The first "LD_{50}" should be "LC_{50}" (page 15, first line of last paragraph).

2.10. Derivation of 'Acceptable/ Tolerable Daily Intakes'

The use of chemical specific adjustment factors (CSAF) should have been mentioned on page 16.

2.11. Completeness of toxicological database

Base-set requirements for new and existing chemicals as described in the report is inaccurate. Missing are i) information on toxicokinetics, and ii) acute toxicity data obtained by exposure to two routes (same comment for chapter 3.5). NB: in the revised TGD more data are required on reproductive toxicity.

Mention about the EU new chemicals policy (REACH) should have been given (page 16).

2.12. Risk assessment for non-threshold effect

The CSTEE points to the fact that, contrary to the statement in the report (page 17), it is possible to identify a tolerable daily intake for substances with non-threshold effects by characterising a virtually safe dose (VSD).

It is not possible for low-dose mathematical extrapolation methods to be truly validated. There is not such a disturbingly wide variation in risk estimates if biologically based models are used (page 18, second paragraph).

Chapter 3. Risk assessment of organic compounds in toys

The chapter describes the assessment of exposure limit for the possible routes of exposure (oral, dermal, inhalation, more than one route) and for chemicals without safety limits.

3.1. Oral exposure

To estimate this route of exposure the data of the CSTEE opinion of 26-27 November 1998 are taken (3hrs per day, 10 cm^2 mouthing area) and the intake is compared to the TDI ($\times$10 to adjust for total intake of a 10 kg child) of which 10% is allocated to the toy. The CSTEE notes that this exposure assessment is a worst-case scenario for toys that may be mouthed by children. Thus, exposures from other toys that are not normally mouthed will often be lower. Also, it should be noted that in the existing substances program a body weight of 8 kg is used (in conformity with the CSTEE). In the report 10 kg is used, but in annex D, Appendix 2 apparently 8 kg is used.

Based on a recent and elaborate mouthing observation study the 3 hr mouthing time default value seems indeed a rather worst case estimate (Kiss, 2001; Greene, 2002). These reports can be found on http://www.cpsc.gov/library/foia/foia02/brief/briefing.html (Petition requesting ban of use of PVC in products).

The CSTEE notes that no scientific basis is given to justify for the value of 10% allocated to the exposure to toys (Page 20, first paragraph).

3.3. Inhalation

The inhalation rates of children from 0-1 year to the age of 5-7 years are taken from the US EPA and a 100% absorption is assumed.

3.4. Exposure for more than one route

Here the calculated data for the different routes of exposure will be added. The CSTEE agrees with the additive approach proposed (page 21).

3.5. Chemicals which do not have safety limits

The CSTEE agrees that in these cases a complete risk assessment with the identification of NOAELs and MOS has to be carried out.

Chapter 4. Assessments of simulants to cover contact routes

4.3. Simulant tests

It is noted that DBDPE (relatively insoluble in water) is either not detected or not tested. The question is why this compound was used in the simulant test.

Chapter 6. The TG-3 Ranking scheme

Description of the Ranking Scheme

The ranking scheme was introduced to identify chemicals that warrant the establishment of standards. This is a first tier of prioritisation without considering exposure and usage information of the toys.

The ranking scheme has been drafted by the Dutch Ministry of Housing, Planning and the Environment. It uses information about classifications under the revised criteria for labeling (Annex VI of Directive 67/548/EEC) to provide a numerical ranking. This scheme considers carcinogenicity, mutagenicity and reproductive and developmental toxicity. Since toys come into contact with skin, sensitisation and severe target organ toxicity were also considered.
The information on classification and other information are taken from reviews by IPCS, IARC, Patty's Industrial Hygiene and Toxicology, and Opinions of SCC (series 1-8, the latest from 1990), NTP.

When limited information was available literature searches in 4 major databases are performed. If sufficient information to rank the chemical was available no further search was conducted.

The rationale of the ranking is described in Table 1 (page 32). The overall ranking is said to be the "highest in any [toxicity] category and/or accumulation across end-point for chemicals in category 9 or 10".

The ranking system is given in Table 1:

Ranking	Hazard indicators (carcinogenicity, reproductive and developmental effects, mutagenicity, sensitisation and severe organ toxicity)
Non classifiable[1]	No information identified in the literature
5	No evidence of effects/definitely not relevant (i.e. data shows no adverse effect in at least mutagenicity, reproductive toxicity and skin sensitisation endpoints).
6	Insufficient data (i.e. insufficient data to evaluate at least the mutagenicity, reproductive toxicity and skin sensitisation endpoints).
7	Limited data of toxic effects (either animal or human) in the above categories.
8	Effects in animals but unlikely to occur in humans (evaluation not definitive).
9	Evidence of effects in animals that **may be** relevant to humans, or evidence to suggest that it occurs in humans.
10	**Clear evidence of effects in humans.**
Overall	Highest in any category and or accumulation across endpoints for chemicals in category 9 or 10.

Although data on exposure and on use pattern are not considered, the approach is acceptable provided it is only used for a preliminary screening to set priorities for further evaluation of the individual chemicals.

The reasoning for starting the ranking from 5 is not explained.

a) It was considered that chemicals with clear or suggestive evidence of potential effects in humans (ranks 9 and 10) should be restricted (not be intentionally added to toys and, if their presence is unavoidable, their concentration should be reduced to as low as reasonably practicable; for these chemicals standards and analytical methods should be developed at the limit of detection). The CSTEE notes that concepts such as "unavoidable" and as low as "reasonably practicable" are not part of risk assessment but of risk management.

b) For chemicals ranked as "not classifiable" or for which insufficient data are available (Rank 6), further information would be sought from industry and from other sources. The amount of additional data sought would depend on the anticipated level of exposure, but in any case would include bacterial mutagenicity, clastogenicity/aneugenicity and mammalian cell mutagenicity (pages 141 and 144). Elsewhere in the Report (pages 3, 70, 84) it is said that substances with insufficient toxicity data should not be present in toys if there is a potential for exposure. However this statement is not made in the subsequent Sections where the Ranking Scheme is discussed, so it is not clear if this is the position formally adopted in the Report.

c) Chemicals with ranking 5 (no evidence of effects/definitely not relevant), 7 (limited data of toxic effects in animals or humans) and 8 (effects in animals but unlikely to occur in humans) will be considered in a second tier risk assessment, which in the view of the CSTEE must include exposure assessment.

[1] Not included in Table 1 page 32

Comments on the Ranking Scheme

i) There is some confusion in the Report about the prioritisation of the chemicals for assessment, possibly because it is made up of Sections written at different times. So it is not clear to the CSTEE where the exercise has reached up to the present time.

ii) Toxicity end-points selected: In some cases the terms "reproductive" and "developmental" are used in a way that does not make it clear whether both were addressed or only one (e.g. page 32, last 2 lines and Table 1). Given the particular population of concern (children), it is important that both reproductive and developmental toxicity should be addressed in all cases. Furthermore, the CSTEE considers that irritancy should also have been considered.

iii) The application of the ranking scheme, specifically with regard to the overall ranking based on "accumulation across end-points for chemicals in category 9 or 10", is not clear (Table 1 page 32).

iv) There is a lack of clarity as to whether all chemicals with inadequate toxicity information are classified as undesirable in toys.

The adequacy of the literature retrieval employed was not appropriate for some chemicals. The ATSDR (U.S. Agency for Toxic Substances and Disease Registry) would have provided additional valuable information (page 32, 2.). Moreover sources of literature are not completely compatible, e.g. for plasticisers. A number of substances mentioned in Annex C are or have been dealt with within the scope of the existing substances regulation. Another important source of information that is not used is the website of the European Chemicals Bureau (same comment for chapter 13).

v) Table 1: The ranking for "Effects in animals but unlikely to occur in humans (evaluation not definitive)" is judged to be too high relative to "Insufficient data (i.e. insufficient data to evaluate at least the mutagenicity, reproductive toxicity and skin sensitisation endpoints") (page 32). The additional category of "not classifiable" might be combined with category 6, which could then read "no or insufficient data".

Analysis on groups of chemicals

7.2 Hazard assessment

Specific comments are given using flame retardants (Chap 7) as example.

The CSTEE notes the following serious inconsistencies:

Discrepancy found for 365 (TBBP-A): overall ranking of 5, as stated here and in annex L (page 234) in contrast with overall ranking of 6 in annex M (page 252) and 9 in Table 2 (page 37). Ranking should be 6 as there are no carcinogenicity data.

Discrepancy found for 375: overall ranking of 8 (as stated here and in annex L) in contrast with overall ranking of 6 in annex M.

Discrepancy found for 392: overall ranking of 9 (as stated here and in annex L) in contrast with overall ranking of 6 in annex M.

Ranking for mutagenicity not consistent when positive in Ames/Salmonella test and no further data available (e.g. 8 for 379 (BMP) and 7 for 380).

Ranking for mutagenicity as 5 solely based on negative Ames/Salmonella and no further mutagenicity data available (e.g. for 362, 369/369bis, 372, 366, 385) is rather premature. The ranking should have been rather 6 (which was done for 811, see page 247) than 5. This is also true for the ranking of reproductive and developmental toxicity as 5 solely based on negative teratogenicity data and no further data available (e.g. for 365, 384).

Overall ranking of 6 for dimethyl phosphonate in annex M (page 258) not understood, given indications for mutagenicity in vitro and in vivo, and for carcinogenicity.

In paragraph d) the rationale is not clear why of the 10 flame retardants ranked as 9, only 6 are specified as a presumed hazard to humans.

7.4. TG 3 Opinion

Table 2 is not consistent with Table 1 (page 35) for 365, 368, 369, 376, 384, 393, and 811.

There is a contradiction in the statements under 2. and 3. Some substances, e.g. 201 and 385, mentioned in Table 2 are also mentioned in Table 3.

Table 4 is not consistent with Table 1 (page 35) where compounds 373 and 383 are classified as 9, and for 365, 368, 369, 376, 384, 393, and 811.

Detailed analysis of a few selected chemicals is given in the Appendix.

REFERENCES

Kiss CT. 2001. A mouthing observation study of children under 6 years of age.Tab F, p 49-210. *In* Petition Requesting Ban of Use of PVC in Products - Intended for Children Five Years of Age (HP 99-1). Part 1-4. U.S. Consumer Product Safety Commission (CPSC).

Greene MA. 2002. Mouthing times among young children from observation data. Tab G, p 212-238. *In* Petition Requesting Ban of Use of PVC in Products - Intended for Children Five Years of Age (HP 99-1). Part 4. U.S. Consumer Product Safety Commission (CPSC).

APPENDIX

DETAILED ANALYSIS OF A FEW SELECTED CHEMICALS

Triphenyl phosphate (TPP) (No 384), CAS No. 115-86-6

TPP was only described in Annex L: Assessment of certain flame retardants. We agree with the overall ranking at 7 based on some equivocal evidence of **sensitisation** in humans without animal data. Cases of skin sensitisation (Clayton and Clayton, 1981-1982) and allergic reactions (Snyder, 1990) have been reported in humans in a patch test at concentrations as low as 0.05 % TPP.

We agree that the **acute toxicity** of TPP is low. In the TOXNET HSDB the LD50 rat (oral) was 3.8 mg/kg (Snyder, 1990), LD50 mouse (oral) 1.32 mg/kg (American Conference of Governmental Industrial Hygienists, 1986), and LD50 for rabbit (dermal) 7.9 mg/kg (Snyder, 1990).

Under **repeat dose** exposure it could be included that the low toxicity observed was a slight depression in growth rates and increased liver weight in rats fed 0.5 % TPP in the diet.

Under the description of the **neurotoxicity** of TPP it could be included that delayed onset of peripheral neuropathy similar to that produced by tri-orto-cresyl phosphate exposure has been seen in experimental animals. This has been reported in the literature (Toxnet HSDB), and should be taken into account:

Experimentally degeneration of motor nerve cells and peripheral nerves has been induced by TPP in animals, and lesions have been observed histologically in the nuclei of the nerves of the extraocular muscles (Grant, 1986).

TPP caused delayed peripheral neuritis involving motor neurons, resulting in a flaccid paralysis, particular of the distal muscle. No sensory disturbances were reported (Grosselin *et al.*, 1984).

TPP is a neurotoxicant in animals. When injected in cats it caused delayed paralysis. Two of 6 cats given a single ip injection of TPP at 0.1 to 0.4 g/kg developed paralysis after 16 to 18 days (Mackinson *et al.*, 1981).

TPP caused generalised delayed illness and paralysis in cats and primates. The observed demyelisation of spinal cord resembled that obtained with tri-orto-cresyl phosphate. Neuromuscular signs were observed above 0.2 g/kg in the cat (Clayton and Clayton, 1981-1982).

Conclusion

The CSTEE agrees with the overall ranking of 7 based on some equivocal evidence of sensitisation in humans without animal data. Under the description of the neurotoxicity of TPP it should be included that delayed onset of peripheral neuropathy similar to that produced by tri-orto-cresyl phosphate exposure, has been seen in experimental animals.

References

American Conference of Governmental Industrial Hygienists. 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. 613.

Clayton GD and Clayton FE (eds). 1981-1982. Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons. 2374.

Grant WM. 1986. Toxicology of the eye. 3rd ed. Springfield, II: Charles C. Thomas Publisher. 943.

Grosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products. 5th ed. Baltimore: Williams and Wilkins. P. II-302.

Mackinson FW, Stricoff RS, Patridge LJ Jr., (eds). 1981. NIOSH/OSHA – Occupational Health Guidelines for Chemical Hazards. DHHS (NIOSH) Publication No. 81-123 (3 Vols). Washington, DC: U.S. Government Printing Office.

Snyder R (ed). 1990. Ethyl Browning's Toxicity and Metabolism of Industrial Solvents. 2nd ed. Volume II. Nitrogen and Phosphorus solvents. Amsterdam-New York-Oxford: Elsevier. 489.

Tris(2-chloroethyl) phosphate (TCEP) (No. 390), CAS No. 115-96-8

TCEP is described in Annex L, Assessment of certain flame retardants, and in Annex M, Further assessment of flame retardants. However, the basis for the rank = 9 is conflicting between Annex L and M. In Annex L the rank = 9 is described to be based on mutagenicity, and in Annex M the rank = 9 is described to be based on effects on fertility and carcinogenicity. A clarification is needed.

No section describing **repeat dose** toxicity is included in Annex L, this is only described in Annex M. In repeat dose studies TCEP caused adverse effects in the brain (hippocampal lesions in rats), liver and kidneys (Environmental Health Criteria, EHC, 209), this should also have been included in Annex L.

For **reproductive and developmental effects** we do not agree with Rank = 5 since TCEP adversely affects fertility in male rats and mice, see studies described below (EHC, 209). The rank should be 9. In Annex M the effects of TCEP on fertility is described, and the effect on fertility is correctly included in the basis for a total score at 9 as can be seen from the studies below:

Mice studies
In a 13 week oral gavage study in mice with doses up to 700 mg/kg bw the absolute epididymis weight and absolute and relative testis weights were decreased, and an increase in the number of sperm with abnormal morphology were reported (Morrissey *et al.*, 1988).
In a continuous breeding study in mice, dosed to TCEP by gavage administration, TCEP decreased the number of litters per pair and the number of live pups per litter in the F_0 generation. Both sexes were affected, however, the males were relatively more sensitive. All sperm endpoints (sperm concentration, motility and morphology) were adversely affected. The data indicated reduced fertility at TCEP doses from 175 mg/kg bw (Gulati *et al.*, 1991).

Rat studies
In a 13 week oral gavage study in rats with doses up to 175 mg/kg bw the sperm motility was reduced (Morrissey et al., 1988).
In an inhalation study male rats were exposed to 0.5 or 1.5 TCEP/m^3 for 4 month. Testicular toxicity was reported at both dose levels including decreased sperm counts, decreased sperm motility and abnormal sperm morphology. Histology of the testes showed increases in spermatogonia with a decreased numbers of germ cells in later stages of development. In the high dose group the fertility was decreased with increased pre- and post-implantation loss (Shepel'skaya and Dyshinevich, 1981).

For **Mutagenicity** we agree with a Rank = 9. In Annex L it is described that the overall ranking at 9 is based on mutagenicity.

As regards the mutagenicity of TCEP the results from the induction of SCE and transformation assay could have been included. TCEP was tested for SCE in V79 cells in two studies at concentrations from 343 to1000 μg/ml (exp. 1) and from 3000 and 3000 μg/l (exp. 2). In the first experiment an increase in SCE was reported from 700 μg/ml with S9 and at 700 μg/ml without S9 (1000 μg/ml was not tested without S9). In the second experiment TCEP was only tested without S9 and was positive at 2000 and 3000 μg/ml, however, cytotoxicity was reported at 3000 μg/ml (Sala *et al.*, 1982). In Syrian hamster embryo cells transformation was observed at concentrations of 400 and 500 μg/ml, higher concentrations (600 and 800 μg/ml) were toxic to the cells and no transformation was seen (Sala *et al.*, 1982).

In the **Carcinogenicity** section in Annex L only studies with mice are described. However, in Annex M it is described that TCEP caused evidence of carcinogenicity in both male and female rats - kidney adenomas (benign tumours) - when administered orally for 2 years. In the EHC, 209 it is described that TCEP causes benign and malignant tumours at various organ sites in rats and mice. A clarification is needed.

Conclusion

The CSTEE agrees with a rank of 9. However, a clarification between Annex L and Annex M is needed related to the basis for a rank of 9. In Annex L this is described to be based on mutagenicity, whereas in Annex M it is based on effects on fertility and carcinogenicity. The effects on fertility should also be described in Annex L. As regards mutagenicity, studies describing the induction of SCE and the cell transformation in Syrian hamster embryo cells should have been included.

References

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Colourants (chap 8)

General comment :

Of the 73 colourants sent to TG3 for evaluation, 13 with sensitizing potential (Table 7) and 24 with suspected CMR properties (Table 8) have been eliminated. The remaining 36 comprises 30 reactive dyes that pose no threat to the consumer (Table 9) and 6 with missing toxicological data (Table 10).
Some of the colourants have been evaluated more specifically in Annexes P and Q but it is not clear why they have been selected.

Single compounds:

Conclusion for Disperse Blue 1 (No. 347), CAS No. 2475-45-8

This dye is correctly listed in Table 8 for its suspected mutagenic and carcinogenic properties being classified in EU Canc. Cat. 2. Due to its R 43 it should also be listed in Table 7 for sensitisation.

Conclusion for Disperse Yellow 3 (No. 351), CAS No. 2832-40-8

According to the NTP-81-80 report (NIH publication No. 82-1778 and a study by NIOSH (PB84-201136) there is indication for a carcinogenic potential. The compound is correctly listed for sensitizing potential in Table 7 but it also requires listing in Table 8 for its CMR properties.

Acid Blue 9 (No. 761), CAS No. 3844-45-09

It is used in cosmetics and therefore recommended for use in toys (Table 9). However, in Annex P: assessment of certain non-azo colourants it is indicated, that IARC classified it as Cat.3 carcinogen because of limited evidence for carcinogenicity in animals. The literature search identified the study of Borzelleca *et al*. (1990) which did not reveal increased cancer incidence in rats and mice "confirming earlier investigations". IARC (1978) based its classification on the study by Rowland *et al*. (1977) on long term toxicity of brilliant blue FCF in mice. Animals received 0, 0.015, 0.15 or 1.5% (0, 20, 200, 2000 mg/kg bwt.) in feed for 80 weeks. In the 200 mg/kg group 7/30 females developed kidney tumors (6 adenoma, 1 adenocarcinoma) as compared to 1 kidney adenoma in the control group. Moreover, there is indication of a weakly positive in vivo UDS test and a positive in vitro UDS-test in rat hepatocytes (Kornbrust and Barfknecht, 1985).

Conclusion

Due to insufficient test design (no negative controls) and possible impurities of the test compound the results are difficult to evaluate. Unless these uncertainties have not been clarified by additional investigations, the CSTEE does not recommend listing Acid Blue 9 in Table 9 (Colourants that may be accepted for toys).

References

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Styrene, No. 16, CAS No. 100-42-05 (Chap 9. Solvents.)

On the basis of the evaluation by IARC (1994) the compound is correctly described as carcinogenic/mutagenic, the latter mainly due to the metabolism of styrene to styrene oxide (Annex S: Assessment of certain solvents, pages 366-369). More recent data on species-species extrapolation and PBPK-modeling have not been considered (Cohen *et al.* 2002, Filser *et al.* 2002, Csanady *et al*. 2003) nor the recent reevaluation by IARC (2002). No further evaluation concerning its use as a solvent in toys is done, nor is it listed in any of the Tables 3-4.
Styrene is listed in table 3: SCF-regulated monomers that could be used for manufacturing of toys under strict regulation (see Chapter 10. Monomers). However, a definition of "strict regulations" is not provided.

References

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IARC (International Agency for Research on Cancer). 2002. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Monographs 82: 437-550.

Formaldehyde, No. 489 , CAS No. 50-00-0 (Chap 10. Monomers)

The compound is classified and labelled as EC carc. Category 3 (R40) and incorporated in table 3: SCF-regulated monomers that could be used for manufacturing of toys under strict regulation. It is also listed in Table 1: List of monomers to be evaluated by TG 3. Due to abundant additional information a re-evaluation of its carcinogenic potential and potency by the EC is urgently recommended by CSTEE. IARC Monographs Supplement 7 (1987) classified it as a Group 2A carcinogen (limited evidence for carcinogenicity to humans).

References

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Toluene

The acute and repeated dose toxicity of the chemical are correctly described and the chemical is correctly ranked 5 for sensitisation. The chemical is also correctly described as non mutagenic and non-carcinogenic (rank 5). On the other hand, as regards reproductive and developmental effects, a ranking of 5 was adopted based on an HSE Toxicity Review of 1989. However, more recent data (da-Silva *et al.,* 1990; Huntington Research Centre, 1992; Ono *et al.,* 1996; Plenge-Pönig and Karmaus, 1996; Thiel and Chahoud, 1997; Hass *et al.,* 1999) provide additional evidence of effects in animals (decrease in sperm count and reduced epididymal weight in rats; effects on litter size, birth weight and behaviour in rats), and humans (limited evidence of the induction of reduced fertility in exposed women), which could justify a ranking of 7 (limited data of toxic effects in animals or humans).

References

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Nitrobenzene

The acute and repeat dose toxicity of the chemical is correctly presented, and a ranking of 5 for sensitising activity is correctly adopted. The ranking of 5 for mutagenicity which is adopted on the basis of negative results in bacterial and mammalian cells as well as in vivo is also correct despite a recently reported detection, by accelerator mass spectrometry (an ultrasensitive method), of liver DNA adducts in mice treated with nitrobenzene at doses as low as 0.1 mcg/kg (Li *et al.*, 2003). The compound is classified by IARC in Group 2B (possibly carcinogenic to humans) and so the ranking of 8 adopted in the Report is justified. Finally for reproductive toxicity a ranking of 9 is correctly adopted, which determines the overall ranking of the chemical.

References

Li H, Wang H, Sun H, Liu Y, Liu K, Peng S. 2003. Binding of nitrobenzene to hepatic DNA and hemoglobin at low doses in mice. Toxicol Lett. 139 (1) : 25-32.

2-Ethoxyethanol

The acute and repeat dose toxicity are correctly summarised, and a ranking of 5 for sensitising potential is correctly adopted. The chemical has given conflicting responses in *in vitro* tests for mutagenicity, including a negative result reported more recently than the 1990 review on which the Report bases its assessment (Hoflack *et al.,* 1995). Although the overall mutagenicity data might have justified a higher ranking than the 5 adopted, in practice this does not affect the Overall Ranking which is determined by the clear evidence of reproductive and developmental effects. The Report's assessment of the reproductive and developmental toxicity of the chemical reflects correctly the available evidence but it is not clear why a ranking of 9 (rather than 10) is adopted when there is clear evidence of effects in humans, nor is it clear how the Overall Ranking of 10 is arrived at.

References

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