Further comments from industry on the Classification of Triethylene Glycol Butyl Ether (TEGBE – CAS no.143-22-6) Regarding Irritation to the eye.

The French competent authority has tabled a classification proposal for this substance (ECB/01/01). Following an initial discussion at the September meeting of the C&L working group , a provisional classification of Xi, R41 was agreed. We understand there was some confusion at the meeting about the composition of the preparations containing TEGBE which was why a final decision was not made. This document clarifies earlier data submitted by industry, contains new data obtained from producers'archives and also includes background information on TEGBE.

Background information on TEGBE

There are five manufacturers in Europe producing TEGBE. TEGBE is not produced in a pure form but as a 'heavies' stream from the production of ethylene glycol mono/di butyl ether. Stream compositions vary between manufacturers but are in the range ~60-90% TEGBE. The remainder of the composition is higher molecular weight polymeric material (tetra ethyleneglycol monobutyl ether, penta etc.) The single largest use for TEGBE is in hydraulic fluids, mainly brake fluids. A small but significant additional application is the use in oil field chemicals (drilling lubricant/additive). There are no other significant uses in Europe. Because it is not produced in a pure form and is used in a small number of brake fluid formulations which are marketed in large volumes, most data is generated on these formulations.

Eye irritancy

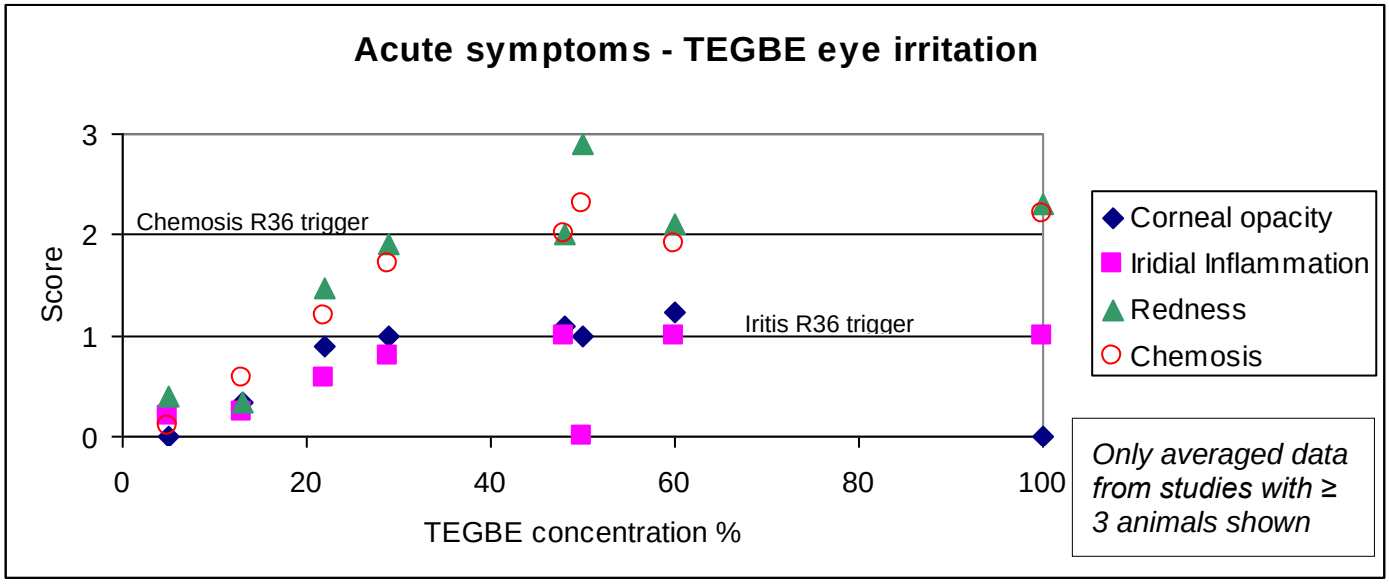
1. It is the revised view of Industry, based on information now available, is that the data is equivocal as to whether pure TEGBE should be classified R36 or R41. This borderline decision is because the only study currently available on purified TEGBE did not show reversibility over the 3 day observation period, despite the fact that the acute effects were not severe. In addition, a test on a production stream ("Solvent 14") of which of which TEGBE is a major component (60-70%), produced a result where one animal still showed symptoms of vascularisation after 21 days. Based on the uncertainties of reversibility, industry accepts that R41 may be appropriate for the pure substance.
2. Four brake fluids from two manufacturers containing concentrations of 5%, 13%, 22%, 29% of TEGBE were tested in a standard OECD 405 guideline GLP studies. The test materials induced corneal opacity, iridial inflammation, and mild to moderate conjunctival irritation, but all scores were below those that would trigger classification as IRRITANT (R36). For the highest concentration formulation, all symptoms had reversed in all three animals within 7 days The results from these studies showed clear dose response relationships for all end points and the length of time for symptoms to disappear. The results provide robust data to support the case that preparations containing TEGBE up to 30% do not warrant labelling even R36.
3. Two further brake fluids from a third manufacturer containing concentrations of 33 and 50% TEGBE respectively were tested for eye irritancy in standard OECD 405 guideline GLP studies. For the formulation containing 33% TEGBE, the screen animal was noted with positive conjunctival and corneal findings. There were no

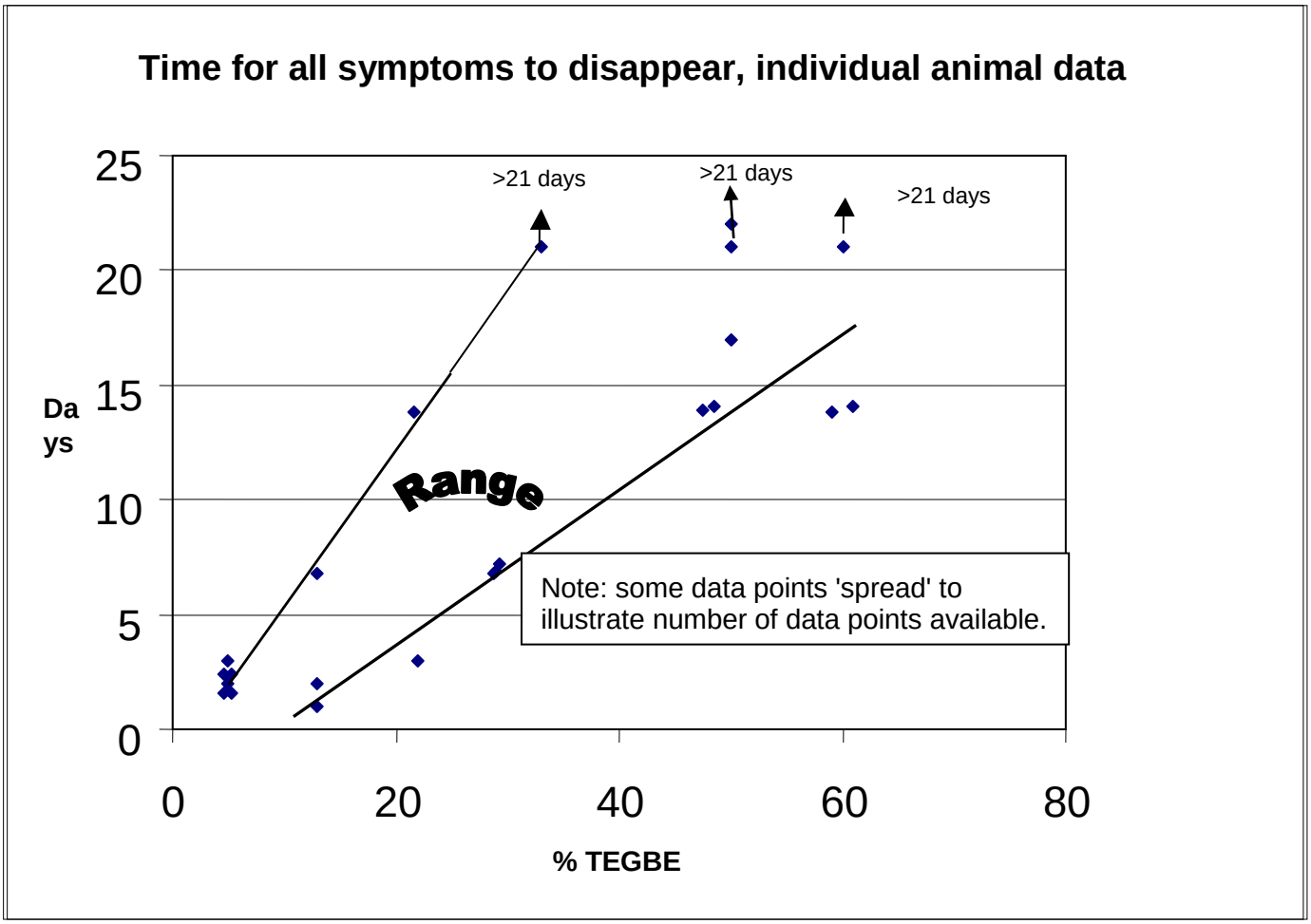
iridal findings. Additionally, corneal neovascularization was noted on study day 7 and persisted through study day 21. Based upon the scores on study day 7, it was decided that no additional animals would be dosed for this study and that the preparation should be classified R41. Scoring for the single animal screen continued according to protocol specifications. Conjunctival irritation and corneal findings were still present at termination (study day 21). The 50% TEGBE formulation also produced significant ocular lesions in 3/3 rabbits; these met the criteria for a classification of R36 but none were sufficiently severe to trigger R41. Minor conjunctival irritation only (grade 1) was still present in two animals at termination (study day 21), however, all irritation had completely subsided by study day 17 for the third animal. These two results are somewhat contradictory but may just reflect statistical variation within the relatively large eye irritation dataset of TEGBE containing formulations.

4. Another preparation containing 48% TEGBE caused iris lesion and conjunctiva chemosis scores of 1 and 2 respectively in 3 NZW rabbits in a standard OECD 405 guideline study. Irritation was fully reversed in 2 animals by day 14 (one animal was humanely killed after the 48h observation period.) The preparation met the criteria for classification IRRITANT R36 only.

It is clear from the data available that the critical effect for eye irritancy classification of TEGBE is reversibility of symptoms rather than the severity of the effects induced. A conservative approach to the limited data available, suggests that R41 would be appropriate for the pure substance. However, the substantial data available for preparations containing TEGBE suggests that the normal default thresholds for preparations containing an R41 substance are not appropriate and would result in overclassification.

A plot of the acute symptoms against TEGBE composition (below) shows a clear concentration/ response relationship:





In addition, a scatterplot above shows the recovery time (complete disappearance of symptoms) for individual animals, where this degree of detail is available; there is evidence for a band with a linear dose response relationship. Note that the lines two lines mark the edges of a range (band) in which recovery times fall.

Conclusions

All studies using formulations with TEGBE concentrations below 30% show acute symptoms which are below the criteria for labelling R36. All animals in all these studies showed full reversal of symptoms within a maximum of 14 days.

Studies using formulations with TEGBE in the range 30 to 60% showed acute symptoms which would warrant labelling such preparations as IRRITANT R36. There is some evidence that symptoms are persistent but that they are eventually reversed (linear dose response relationship.) Of the 10 animals involved in tests with such formulations, 6 fully recovered within the test period, two showed vascularisation after 21 days, one showed mild residual corneal and irritation effects and one was humanely destroyed after 2 days. Industry believes the evidence overall supports R36 for such formulations. It is also clear that studies above 30% TEGBE produce more variable results.

Above 60%, the same classification as for pure TEGBE would be appropriate, based on the lack of data available to support any other conclusions.

Use of the standard thresholds for R41 would lead to confused and very different labelling between historically animal tested products and untested formulations which follow the calculation method of classification.

Oxygenated Solvents Producers Association

CEFIC

Studies provided

Study/Formulation	Study report identification	TEGBE concentration in formulation	Current self classification
Polysolve TB (MB75-990).	MB Research Ltd	100%	R36
Solvent 14	Safepharm report 222/89	60%	R36
Emkadixol 360	WIL-95057	50%	R36
	Safepharm report 548/7	48%	R36
Emkadixol 310	WIL- 95056	33%	R41*
Brake fluid 26 dot 4 (formulation a)	Safepharm report 222/098	29%	Not classified
Brake fluid 26 dot 4 (formulation c)	Safepharm report 222/099	22%	Not classified
Brake fluid 7 dot 4	Safepharm report 222/100	13%	Not classified
Brake fluid dot 4	Shell report SBGR.92.011	5%	Not classified

*based on acute reaction of single animal which did not show reversibility of corneal effects by day 21.