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EXPERT REVIEW

Carcinogenicity of 1,2-Dichloropropane – Review of Information

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Introduction:

The Sponsor asked for an opinion regarding the proposed classification of 1,2-dichloropropane as a Cat.2 Carcinogen, based on a publication by Umeda *et al* 2010.

Activity and Findings:

The publication and evidence for carcinogenicity was reviewed in regard to the category 2 classification proposal. We have taken advice from histopathology experts regarding the findings observed in this study and the possibilities to oppose the proposed classification.

The dose selection, exposure system, animals used and the statistical procedures were all standard and fully acceptable for a toxicology study. The study design can not be criticised.

The incidence of tumours was enough for a classification of the test item as carcinogenic (see below Table 3 from the Japanese publication). In addition to the tumours, the incidence of what may be referred to as pre-neoplastic changes was high, confirming the apparent carcinogenic activity of the test item.

In this type of study, if the degree of irritation is too high, then the tumour formation can be secondary to the chronic irritation effect over a long duration. If the membranes are severely disrupted, then the tumours can be claimed to be not related to the chemical effect on the cells, but a secondary effect of chronic irritation. If the exposure in the study exceeded the MTD (Maximum Tolerated Dose) then the carcinogenicity claim could be disputed. The histopathology of the relevant tissues with details of the degree of irritation is given below (see Table 2 from the Japanese publication).

Table 3. Number of rats bearing the selected histopathological lesions of the nasal cavity in the rats exposed by inhalation to DCP or clean air for 2 years.

	Male				Peto	Female				Peto
Group (ppm)	0	80	200	500	test	0	80	200	500	test
Number of animals examined	50	50	50	50		50	50	50	50	
Neoplastic lesions										
Papilloma	0	0	3	15##	↑↑	0	0	0	9##	↑↑
Esthesioneuroepithelioma	0	2	1	0		0	0	0	0	
Total nasal tumors	0	2	4	15##	↑↑	0	0	0	9##	↑↑
Pre-neoplastic lesions										
Hyperplasia:	0	31**	39**	48**		2	21**	39**	48**	
transitional epithelium		[1.1]	[1.1]	[1.8]		[1.0]	[1.2]	[1.1]	[1.5]	
Squamous cell hyperplasia	0	2	6*	27**		0	0	3	20**	
		[1.0]	[1.0]	[1.1]				[1.0]	[1.3]	
Total pre-neoplastic lesions	0	31**	39**	50**		2	21**	39**	48**	
Non-neoplastic lesions										
Squamous cell metaplasia:	5	31**	41**	49**		3	15**	37**	46**	
respiratory epithelium	[1.0]	[1.0]	[1.0]	[1.2]		[1.0]	[1.0]	[1.2]	[1.5]	
Inflammation:	20	35**	47**	47**		10	30**	39**	40**	
respiratory epithelium	[1.0]	[1.0]	[1.0]	[1.2]		[1.0]	[1.0]	[1.0]	[1.1]	
Atrophy:	0	48**	50**	49**		0	50**	50**	50**	
olfactory epithelium		[1.1]	[1.9]	[2.0]			[1.0]	[1.9]	[2.0]	

Note: The values in brackets indicate the averaged severity grade index of the lesion in affected animals, according to the following equation. [Σ(grade × number of animals with grade)]/number of affected animals. Grade: "slight" scored as 1, "moderate" as 2, "marked" as 3, and "severe" as 4. Significant difference: *$p \leq 0.05$; **$p \leq 0.01$ by χ^2-test, #$p \leq 0.05$; ##$p \leq 0.01$ by Fisher's Exact test ↑: $p \leq 0.05$, ↑↑: $p \leq 0.01$ by Peto's test.

Table 2. Number of rats bearing the selected histopathological lesions and their severities in the rats exposed by inhalation to DCP or clean air for 13 wk.

	Male						Female					
Group (ppm)	0	125	250	500	1000	2000	0	125	250	500	1000	2000
Number of animals examined	10	10	10	10	10	10	10	10	10	10	10	9[a]
Nasal cavity												
Hyperplasia:	0	10**	10**	10**	10**	10**	0	7**	10**	9**	10**	9**
respiratory epithelium		[1.0]	[1.3]	[1.3]	[2.0]	[2.0]		[1.0]	[1.0]	[1.0]	[1.2]	[1.1]
Inflammation: respiratory epithelium	0	0	2	4	8**	8**	0	0	0	0	3	4
Atrophy:	0	10**	10**	10**	10**	10**	0	10**	10**	10**	10**	9**
olfactory epithelium		[1.0]	[1.2]	[1.5]	[2.2]	[2.7]		[1.0]	[1.0]	[1.1]	[1.0]	[2.1]
Liver												
Swelling: centrilobular	0	0	0	0	0	9** [1.0]	0	0	0	0	1	6** [1.8]
Spleen												
Deposition of hemosiderin	0	0	0	1	10**	10**	0	0	4	10**	10**	9**
Increased extramedullary hematopoiesis	0	0	0	0	10**	10**	0	0	0	1	8**	9**
Bone marrow												
Increased hematopoiesis	0	0	0	1	10**	10**	0	0	0	0	10**	9**
Adrenal gland												
Fatty change	0	0	0	0	0	1	0	0	0	0	2	9**

Note: The values in brackets indicate the averaged severity grade index of the lesion in affected animals, according to the following equation. [Σ(grade × number of animals with grade)]/number of affected animals. Grade: "slight" scored as 1, "moderate" as 2, "marked" as 3, and "severe" as 4.
[a]Number of female rats examined were 9 instead of 10, because one rat died before the end of the 13-wk exposure period. Significant difference: $*p \le 0.05$; $**p \le 0.01$ by χ^2-test.

Review of Data:

There is evidence of long-term damage and repair of the nasal mucosa, although the report does not give enough detail to understand fully the exact location within the nasal passage, or all the cell types involved. However, the degree of damage cause by the test item did not cause any ulcers or affect the life span of the test animals. From the tables and text provided inn the publication, I conclude that although there was atrophy and inflammation in the nasal cavity mucosa, the severity was not sufficient to claim that the MTD has been exceeded.

Opinion:

Under these circumstances, the publication does appear to support the argument for a Cat. 2 Carcinogen.

The only way to make a solid argument against this decision would be to make a full review of the histopathological slides by a very experienced histopathologist, then to get a panel of expert pathologists to review relevant slides. This is a major undertaking, requiring a budget of several hundred thousand Euros. The chances of success are small, and the access to the slides for the study may not be possible. My advice is that it is not practicable to make such an undertaking.

The conclusions from the Japanese publication are copied below:

Conclusions

Thirteen-week inhalation exposure of male and female rats to DCP at five different concentrations up to 2000 ppm induced cytotoxic lesions in the nasal cavity, hemolytic anemia, and lesions of liver and adrenal gland. Two-year inhalation exposure of male and female rats to DCP at three different concentrations up to 500 ppm was found to significantly and dose-dependently increase incidences of total nasal tumor including papillomas and esthesioneuroepitheliomas and nasal preneoplastic lesions. These results demonstrate that DCP is a nasal carcinogen in rats. Lifetime cancer risks for humans exposed to DCP in the ambient air, using a non-threshold approach, and in the work environment, using both nonthreshold and threshold approaches, were quantitatively estimated with the data obtained from the present 2-year inhalation study. This paper provides novel information about inhalation carcinogenicity and toxicity of DCP and their dose-response relationships for reconsideration of the current OEL.

From Umeda *et al* 2010.

SUMMARY:

The Sponsor asked for an opinion regarding the proposed classification of 1,2-dichloropropane as a Cat.2 Carcinogen, based on a publication by Umeda *et al* 2010.

The publication and evidence for carcinogenicity was reviewed in regard to the category 2 classification proposal. The evidence from the report supports the classification proposed. It would probably not be practicable to make a solid scientific argument that could prevent the decision being accepted.

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