IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Some Industrial Chemicals
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A working group of 28 experts from 12 countries met in Lyon to evaluate or re-evaluate the evidence for carcinogenicity of sixteen industrial chemicals, all of them organic compounds. These included some aromatic amines (*ortho*-toluidine, 4-chloro-*ortho*-toluidine, and 5-chloro-*ortho*-toluidine), some ethanolamines (di- and triethanolamine and *N*-nitrosodiethanolamine), and three esters [di(2-ethylhexyl) phthalate (DEHP), di(2-ethylhexyl) adipate, and cinnamyl anthranilate]. Most of these chemicals had been assigned high priority for review by a recent Ad-hoc Advisory Group on Priorities (September 1998; IARC Internal Report No. 98/004, available on this website). Seven of the sixteen compounds had been previously evaluated by the IARC Monographs Programme. Evaluations of carcinogenicity, and the most recent previous evaluations, are summarized in Table 1.

For *ortho*-toluidine, evidence for increased risk of cancer in exposed humans had increased from inadequate to limited since the previous evaluation, and this compound was upgraded to *probably carcinogenic to humans* (Group 2A). 4-Chloro-*ortho*-toluidine remained in Group 2A as before. Glycidol was evaluated for the first time and classified in Group 2A on the basis of sufficient evidence for carcinogenicity in experimental animals, supplemented by other relevant data concerning the mode of carcinogenic action of this chemically reactive epoxide.

Four compounds which were evaluated for the first time, including 2,2-bis (bromomethyl) propane-1,3-diol, 2,3-dibromopropan-1-ol, ethylbenzene, and nitromethane, were classified as *possibly carcinogenic to humans* (Group 2B) on the basis of sufficient evidence for carcinogenicity in experimental animals but inadequate evidence for cancer in exposed humans. For eight compounds, including 5-chloro-*ortho*-toluidine, coumarin, pyridine, **diethanolamine,** triethanolamine, di(2-ethylhexyl) adipate, and cinnamyl anthranilate, **evidence for cancer in humans was inadequate and evidence for carcinogenicity in experimental animals was limited or inadequate. These were considered *not classifiable as to carcinogenicity to humans* (Group 3).** *N*-Nitroso-diethanolamine, which can readily be formed from either di- or triethanolamine in the presence of inorganic nitrite, is carcinogenic in experimental animals and remained classified in Group 2B.

DEHP belongs to a structurally diverse group of compounds that induce peroxisome proliferation in the liver in mice and rats, but not in other rodent and non-rodent species that have been tested and not in human liver tissue. DEHP causes tumors of the liver in mice and rats, but at no other site, and had previously been classified as *possibly carcinogenic to humans* (Group 2B). The working group considered that in light of a large body of other relevant data, including evidence from genetically engineered mice, DEHP met criteria previously established for evaluation of such substances (IARC Technical Report No. 24, 1995; Consensus Report available on this website). DEHP was downgraded from Group 2B to Group 3, *not classifiable as to carcinogenicity to humans.* In making its overall evaluation of the possible carcinogenicity to humans of DEHP, the working group took into consideration that (a) DEHP produces liver tumors in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (b) peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of DEHP in mice and rats; and (c) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to DEHP nor in the livers of exposed non-human primates. Therefore, the mechanism by which DEHP increases the incidence of hepatocellular tumors in rats and mice is not relevant to humans.

While both di(2-ethylhexyl) adipate and cinnamyl anthranilate also cause peroxisome proliferation in the liver in mice and rats, evidence that these compounds are carcinogenic in experimental animals is less than sufficient. Thus considerations of mechanism or mode of action of these compounds played no role in their classification by this working group.

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TABLE 1
IARC MONOGRAPHS WORKING GROUP - VOLUME 77:
SOME INDUSTRIAL COMPOUNDS

Agent	Previous Evaluation			Current Evaluation		
	Degree of Evidence in Humans	Degree of Evidence in Animals	Overall Evaluation	Degree of Evidence in Humans	Degree of Evidence in Animals	Overall Evaluation
2,2-Bis(bromomethyl) propan-1,3-diol				I (ND)	S	2B
4-Chloro-*ortho*-toluidine	L	S	2A	L	S	2A
5-Chloro-*ortho*-toluidine				I (ND)	L	3
Cinnamyl anthranilate	I (ND)	L	3	I (ND)	L	3
Coumarin	I (ND)	L	3	I (ND)	L	3
2,3-Dibromopropan-1-ol				I (ND)	S	2B
Diethanolamine				I	L	3
Di(2-ethylhexyl) adipate	I (ND)	L	3	I (ND)	L	3
Di(2-ethylhexyl) phthalate	I (ND)	S	2B	I	S	3*
Ethyl benzene				I	S	2B
Glycidol				I (ND)	S	2A*
Nitromethane				I (ND)	S	2B
N-Nitrosodiethanolamine	I (ND)	S	2B	I	S	2B
Pyridine				I	L	3
Ortho-Toluidine	I	S	2B	L	S	2A
Triethanolamine				I	I	3

S = sufficient evidence of carcinogenicity
L = limited evidence of carcinogenicity
I = inadequate evidence of carcinogenicity
ND = no data
Group 1 = carcinogenicity to humans;
Group 2A = probably carcinogenic to humans
Group 2B = possibly carcinogenic to humans
Group 3 = cannot be classified as to its carcinogenicity to humans
*Other relevant data taken into consideration