資料６

1，2-ジクロロプロパンに関する文献調査結果の概要について

１　新たに収集・参照した文献（主なもの）

文献１　U.S.NTP (1986), NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,2-Dichloropropane (Propylene Dichloride)(CAS NO.78-87-5)(NTP：National Toxicology Program アメリカ国家毒性プログラム）

文献２　IPCS(1993), Environmental Health Criteria,146 1,3-Dichloropropene, 1,2-Dichloropropane and Mixtures (PART B 1,2-Dichloropropane) 1993(IPCS：International Programme on Chemical Safety 国際化学物質安全性計画　世界保健機関 WHO の決議に基づくもの）

文献３　Jones,A.R.and Gibson,J.(1980), 1,2-Dichloropropane:metabolism and fate in the rat.

文献４　Bartels,M.J.and Timchalk,C.(1990), 1,2-Dchloropropane:investigation of the mechanism of mercapturic acid formation in the rat.

文献５　Timchalk,C.et al. (1991), Disposition and metabolosim of [^{14}C]1,2-dichloropropane following oral and inhalation exposure in Fischer 344 rats.

文献６　Klaassen,C.D.,ed.(2001), Casarett and Doull’s Toxicology　The Basic Science of Poisons Sixth Edition

文献７　Guengerich,F.P.,et al,(1992), Elucidation of Catalytic Specificities of Human Cytochrome P450 and Glutathione S-Tranferase Enzymes and Relevance to Molecular Epidemiology.

文献８　OECD SIAM , OECD SIDS 1,2-Dichloropropane　CAS No：78-87-5　November 2003 (OECD SIAM：OECD が行っている高生産量物質のハザードアセスメント(SIDS)の初期評価会議）

２　収集・参照文献から得られた情報

（１）発がん性（文献１）

The short chain halogenated hydrocarbons are widely used in agriculture and industry. The toxicity, carcinogenicity, and mutagenicity of the chemicals in this class varies widely (Van Duuren, 1977; Weisburger, 1977; Fishbein, 1979; IARC, 1979; Chu and Milman, 1981). The direct acting carcinogens in this class include the epoxides and the halo ethers; the indirect acting compounds (those requiring metabolic activation) may be metabolically activated to the ultimate carcinogen in tissues such as the liver, stomach, lung, or kidney (Van Duuren, 1977). Epoxide interrmediates are demonstrated metabolites of trichloroethylene (epoxy-1,1,2-trichlorethane), allyl chloride (epichlorohydrin and glycialdehyde), and 1,2-dibromo-3-chloropropane

(epichlorohydrin and glycialdehyde) (Van Duuren,1977). Some of the halogenated hydrocarbons, such as l ,2-dibromomethane and 1, 2-dichloroethane, are thought to be direct alkylating agents (Chu and Milman, 1981). DCP is reportedly metabolized to 1,2-epoxypropane (Jones and Gibson, 1980). DCP has not been shown to have any direct alkylating activity, while the metabolite 1,2-epoxypropane has been shown to be an alkylating agent (Jones and Gibson, 1980). The role of metabolic activation in DCP toxicity is not clear.（P46）

（２）代謝

ア（文献２）1,2-Dichloropropane is metabolized to form a variety of metabolic products. Dichloropropane oxidation yielded the mercapturic acid, *N*-acetyl- *S*-(2-hydroxypropyl) cysteine (Jones & Gibson, 1980). Three mercapturic acid metabolites were identified in the urine of Fischer 344 rats (110-140 g) administered 1,2-dichloropropane orally (100 mg/kg body weight) or by inhalation (466mg/m^3 per 6 h). These compounds are *N*-acetyl-*S*-(2-hydroxypropyl)-L-cysteine, *N*-acetyl- *S*-(2-oxopropyl)-L-cysteine and *N*-acetyl- *S*-(1-carboxyethyl)-L-cysteine. Fischer 344 rats were given a single oral dose of deuterium (D6)-labelled dichloropropane (105 mg/kg body weight) in a mechanistic study conducted to determine whether the conjugated metabolites are generated through a sulfonium ion intermediate. The results suggest that dichloropropane undergoes oxidation either prior to, or subsequent to, glutathione conjugation. There was no evidence to support the existence of a sulfonium intermediate in the formation of the 2-hydroxypropyl -mercapturic acid metabolite of dichloropropane (Fig. 8). Instead, this metabolite is thought to arise via the direct oxidation of 1,2-dichloropropane, either prior to, or following, conjugation with glutathione (Fig. 8) (Timchalk et al., 1989; Bartels & Timchalk, 1990).（P17～18）

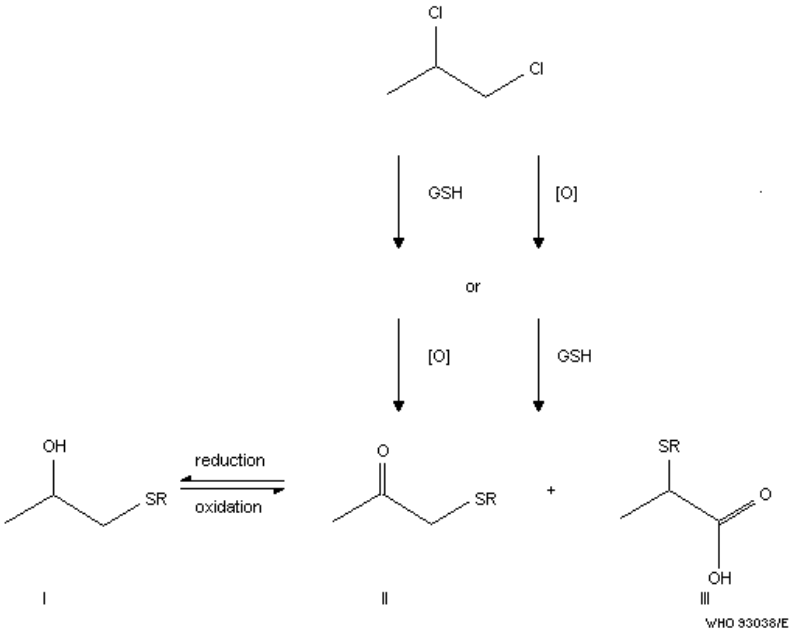

Fig. 8. Proposed metabolic scheme for the formation of mercapturic acid metabolites of 1, 2-dichloropropane in the rat.

I = N-acetyl-S-(2-hydroxypropyl)-L-cysteine;
II = N-acetyl-S-(2-oxopropyl)-L-cysteine;
III = N-acetyl-S-(1-carboxyethyl)-L-cysteine.
Adapted from: Bartels & Timchalk (1990).

イ（文献２）Both 1-chloro-2-hydroxypropane (II) and 1,2-epoxypropane (III) are proposed as intermediates in the metabolism to the mercapturic acid. 1,2-Epoxypropane can also be metabolized to propanediol (IV), which is further metabolized to pyruvate and enters the tricarboxylic acid cycle; carbon dioxide is released and expired. Epoxypropane may also be conjugated with glutathione (VI) and excreted in the urine. Jones & Gibson (1980) further proposed that the 1-chloro-2-hydroxypropane (II) may be metabolized to beta-chlorolactaldehyde (VII) and beta-chlorolactate (VIII) (Fig. 9).（P19）

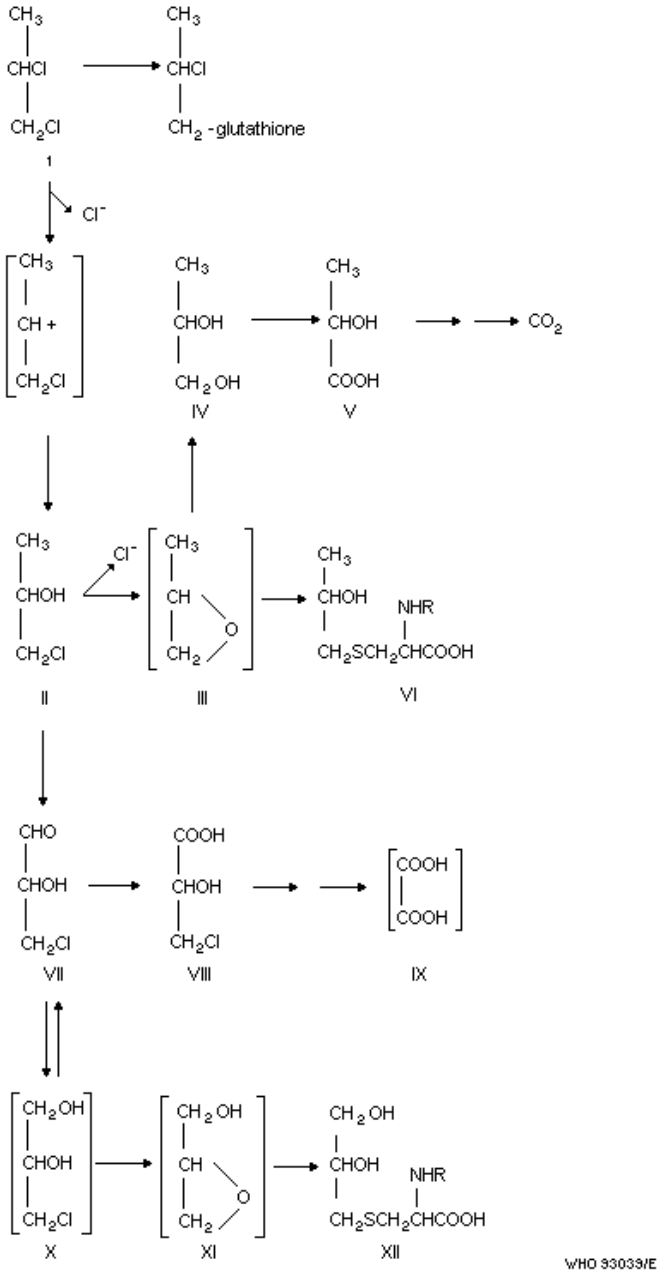

Fig. 9. The proposed metabolic pathways of 1, 2-dichloropropane in the rat. Compounds in parentheses are proposed intermediates. From: Jones & Gibson (1980).

ウ（文献３）When either 1,2-dichloropropane or 1-chloro-2-hydroxypropane were incubated with rat liver supernatants and exogenous glutathione for 2h,there was no decrease in the thiol content of the medium.Pre-incubation of these substrates for up to 3h with the supernatant before addition of glutathione produced a slight though not significant fall in thiol concentration. With 1,2-epoxypropane as substrate,thiol levels fell by approx .30% in the first hour of incubation at 20℃. This indicates that the alkylating ability of the chlorinated

substrates towards glutathione *in vitro* is low, but that of 1,2-epoxypropane is relatively high.（P840）

The major dedotoxicative pathway for 1-chloro-2-hydroxypropane is 1,2-epoxypropane （Ⅲ） which can either conjugate or be hydrolysed to propane -1,2-diol（Ⅳ）.Conjugation would lead to the ultimate excretion of *N*-acetyl- *S*-(2-hydroxypropyl) cysteine （Ⅵ） in the urine,whereas hydrolysis to propane -1,2-diol and oxidation of this to lactate（Ⅴ）would lead toits complete oxidation to CO_2 in the tricarboxylic acid cycle.（P844）

In mammalian systems, epoxides are either alkylated by glutathione (Fjellstedt et al.1973,Boyland and Williams 1965) or are converted to the more polar vicinal diols (Lu et al.1977).（P845）

エ（文献４）The proposed metabolic scheme for the formation of these DCP metabolites is shown in figure 4.Oxidation of the 1-position of the parent compound and subsequent GSH conjugation would give rise to the 1-carboxyethyl mercapturate Ⅲ.This pathway was also proposed by Zoetemelk et al.(1986), for the formation of Ⅲ from 1,2-dibromopropane. Similar conjugation at the terminal carbon of DCP and oxidation would result in Ⅱ. Reduction of this mercapturate could then give rise to the 2-hydroxypropyl mercapturate Ⅰ.（P1040）

オ（文献５）A proposed metabolic scheme is depicted in Fig.3. Three *N*-acetyl cysteine conjugates of DCP were identified in the urine and appear to be result of both glutathione conjugation and oxidative metabolic pathways. Studies using D_6-DCP suggest that the parent compound undergoes oxidation, either prior to/or following conjugation with glutathione to afford Ⅱ and Ⅲ. Enzymatic reduction of Ⅱ would then yield the mercapturate Ⅰ. The oxidation of DCP to lactate would result in the formation of CO_2 and acetyl-CoA, which could then enter the tricarboxylic acid cycle resulting in further metabolism to CO_2.（P305）

In conclusion, [^{14}C]DCP was readily absorbed, metabolized and excreted regardless of route of exposure and there were no sex related differences in the pharamacokinetics and/ 1 or metabolism of [^{14}C]DCP in the rat. However , a dosedependent saturation of metabolism was evident. In addition, the major urinary metabolites as a group were identified as three *N*-acetylcysteine conjugates of [^{14}C]DCP.（P305）

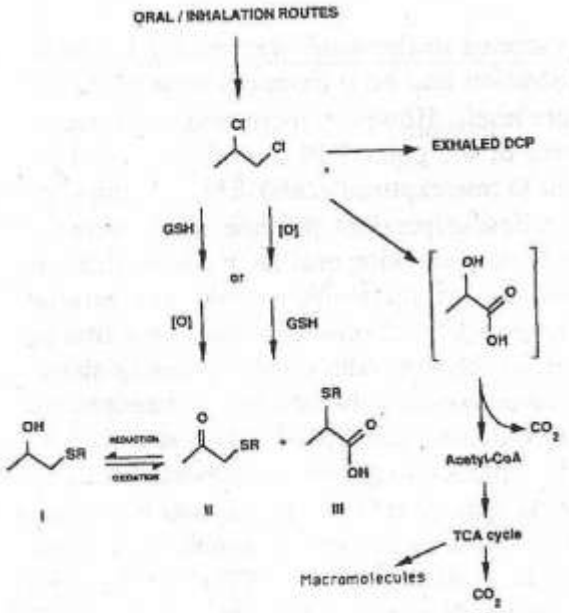

Fig. 3. Proposed metabolic scheme for 1,2-dichloropropane in the rat (R = *N*-acetylcysteine).

（３）DNA 反応性・発がん性と関係する化学物質構造（文献６）

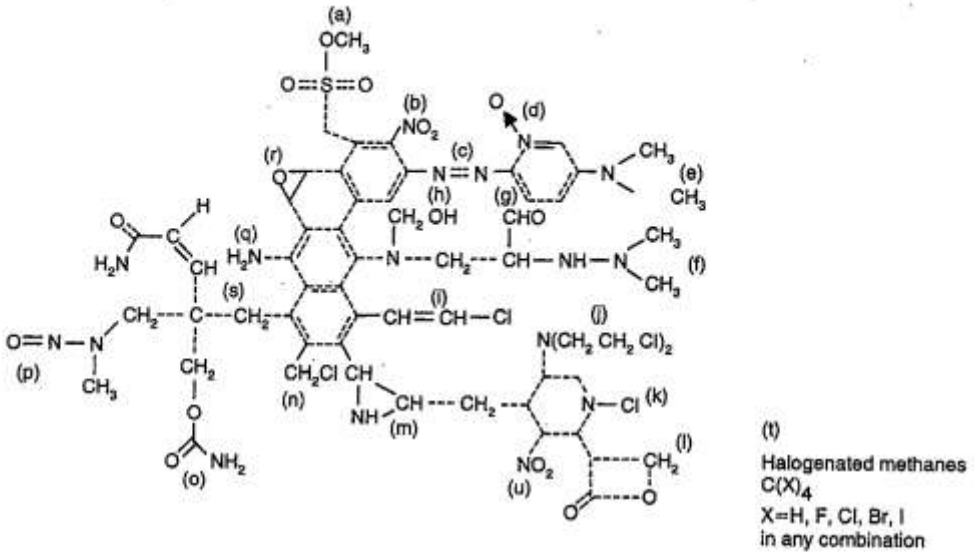

Figure 8-9. The substituents are as follows: (a) alkyl esters of either phosphonic or sulfonic acids; (b) aromatic nitro groups; (c) aromatic azo groups, not per se, but by virtue of their possible reduction to an aromatic amine; (d) aromatic ring, N-oxides; (e) aromatic mono and dialkylamino groups; (f) alkyl hydrazines; (g) alkyl aldehydes; (h) N-methylol derivatives; (i) monohaloalkenes; (j) a large family of N and S mustards (β-haloethyl); (k) N-chloramines (see below); (l) propiolactones and propiosultones; (m) aromatic and aliphatic aziridinyl derivatives; (n) both aromatic and aliphatic substituted primary alkyl halides; (o) derivatives of urethane (carbamates); (p) alkyl-N-nitrosamines; (q) aromatic amines, their N-hydroxy derivatives and the derived esters; (r) aliphatic and aromatic epoxides.

The *N*-chloramine substructure (k) has not yet been associated with carcinogenicity, but potent genotoxic activity has been reported for it (discussed in Ashby et al., 1989). Michael-reactive α,β-unsaturated esters, amides, or nitriles form a relatively new class of genotoxin (e.g., acrylamide). However, the structural requirements for genotoxicity have yet to be established, and this structural unit is not shown in the figure. [Adapted from Tennant and Ashby (1991), with permission of the author and publisher.]

（４）ほ乳動物に対する変異原性（文献２）

In cytogenetic studies using Chinese hamster ovary cells, 1,2-dichloropropane (99.4%) caused both chromosome aberrations and sister chromatid exchanges. Dose levels tested were 0.46-1.50 and 0.113-1.13 mg/ml, respectively (Galloway et al., 1987). （P28）

Priston et al. (1983) also studied the ability of 1,2-dichloropropane (containing 65% 1,2-dichloropropane and 25% 1,3-dichloropropane) to induce chromosome damage using rat liver (RL_4) cells, in concentrations of 5-20 µg/ml. An indication for a small increase in the frequency of chromatid gaps, chromatid and chromosome aberrations, was noticed, but only in the presence of cytotoxic effects. The Task Group considered this study inadequate. （P28）

Von der Hude et al. (1987) used the Sister Chromatid Exchange test *in vitro* in Chinese hamster V79 cells to evaluate the effect of 1,2-dichloropropane (99%). The concentrations tested were 0 (DMSO), 1.0, 3.3, and 10.0 mmol/litre without S9 mix. A dose-related increase in SCEs was observed. With S9 mix and the same concentrations, the SCEs frequency was increased but was less than without S9 mix. （P29）

（５）動物発がん実験（文献２）

ア Groups of 7 to 9-week-old hybrid $B_6C_3F_1$ mice (50 males and 50 females) were administered 0, 125, or 250 mg 1,2-dichloropropane (99.4%)/kg body weight, in corn oil, by gavage, 5days/week for 113 weeks. No influence on growth was observed. The survival of the female animals at the highest dose level was significantly decreased. The incidence of non-neoplastic lesions showed lesions of the spleen (haemosiderosis and haematopoiesis were increased) in female mice at the highest dose level. （P30）

The incidences of neoplastic lesions are summarized in Table 21.（ P39）

On the basis of the results of this study, the NTP concluded that 1,2-dichloropropane induces an increased incidence of liver tumours in male and female $B_6C_3F_1$ mice (Haseman et al., 1984; NTP, 1986). However, the Task Group noted that the incidences of liver adenomas and carcinomas in the treated groups were within the historical ranges of this species (Haseman et al., 1985). The increased incidence of thyroid tumours is equivocal. （P30）

イ Groups of 50 male and 50 female F344/N rats (aged 7-9 weeks)were administered, by gavage, 0, 125 or 250 (female) and 0, 62, or 125 mg (male) 1,2-dichloropropane (99.4%)/kg body weight, in corn oil, 5 days/week for 103 weeks. The highest dose level showed growth depression in both sexes. Survival of female rats at the high dose level was significantly lower.

The incidence of non-neoplastic lesions was not significantly different from that in the controls, except for an increased incidence of foci of clear cell change and of necrosis in the liver in high-dose female rats.（P30）

The incidences of neoplastic lesions are summarized in Table 22.（P40） Apart from these tumours, squamous cell papillomas of the forestomach were found in 1 control male and 1 female rat. In high-dose females, there was an increased incidence of mammary gland adenocarcinomas, but not of mammary gland adenomas. Apart from these tumours, squamous cell papillomas of the fore-stomach were found in two high-dose females (not significantly increased compared to controls). There were no effects on tumour incidences in male rats (Haseman et al., 1984; NTP, 1986). （P31）

（６）肝臓に対する影響に係る研究報告（文献２）

ア Groups of 5 male Wistar rats (200 g) were administered, i.p., 0, 10, 25, 50, 100, 250, or 500 mg 1,2-dichloropropane (97%)/kg body weight, in corn oil, for 5 days (once daily) or for 4 weeks (five days/week), or a single dose of 0, 50, 100, or 250 mg/kg body weight, to investigate the biochemical and histological liver changes. Reduced glutathione (GSH), glutathione-*S*-transferase, cytochrome P450, and protein contents were measured. （P31）

Table 22. The incidence of neoplastic lesions in a rat study with 1,2-dichloropropanea（P40）

A dose-dependent decrease in liver-reduced glutathione was observed after a single injection and a dose-dependent increase after 4 weeks. The liver biochemical pattern after 4 weeks, characterized by a decrease of cytochrome P450 and by an increase in reduced glutathione and glutathione- *S*-transferase activity, suggests a hyperplastic evolution of the liver cells, probably a repair mechanism induced by the early depletion of glutathione. Histologically, the alterations confirm the regenerative nature (atypical mitosis and hyperplastic nodules) of the changes (Trevisan et al., 1989). （P31）

イ The hepatotoxicity of 1,2-dichloropropane (97%) in adult male Wistar rats (5 per group) was studied following daily i.p. injection at dose-levels of 0, 50, 100, 250, or 500 mg/kg body weight per day, in corn oil, for 4 weeks. Biochemical changes in the liver were demonstrated. Significant findings included reduction of aminopyrine demethylase activity at 100 mg/kg or more, increased levels of reduced glutathione and glutathione- *S*-transferase activity at 50 mg/kg or more, and decreased cytochrome P450 activity at 500 mg/kg. The activity of aniline hydroxylase was not affected. Duplicate groups of rats treated with 1,2-dichloropropane, but

allowed a period of 4 weeks of recovery before being subjected to examination, showed that the induced biochemical changes in the liver were completely reversible (Trevisan et al., 1991). （P32）

ウ　1,2-Dichloropropane toxicity is actually preferentially mediated by GSH depletion. This is suggested by the fact that GSH loss is correlated with an increase in the biochemical indices of liver and renal injury, and with the extent of haemolysis. （P32）

エ　Pretreatment of 1,2-dichloropropane-intoxicated rats with buthionine-sulfoximine (BSO) (depleting GSH) markedly increased the overall mortality. Furthermore, the administration of the GSH precursor *N*-acetyl-cysteine (NAC), preventing GSH depletion,reduced the damage in target tissues, as demonstrated by a smaller increase in some biochemical indices of cell injury and a smaller degree of haemolysis. A possible explanation for these findings is that, when the GSH level falls below a certain threshold value, irrespective of the causative agent, a series of common reactions is triggered, inducing peroxidation of membrane lipids, disturbances of Ca_2 homeostasis, and DNA damage, which quickly lead to irreversible liver injury. Furthermore, it is also possible that electrophilic metabolites of 1,2-dichloropropane, formed in the absence of GSH, could directly attack a variety of cell macromolecules the function of which is essentially to ensure the physiological survival of the hepatocytes (Mitchell et al., 1973; Bellomo & Orrenius, 1985; Casini et al., 1987; Orrenius et al., 1989). （P32）

オ　Male Wistar rats were exposed (by gavage) to a single oral dose of 55 mg 1,2-dichloropropane/kg body weight in propylene glycol. The animals were killed 1-6 days after exposure. Glutathione (GSH), lipid peroxidation and protein of liver homogenate were measured. Reduction of hepatic GSH and total protein and enhanced hepatic lipid peroxidation still persisted 6 days after 1,2-dichloropropane administration (Di Nucci et al., 1988). （P32）

Groups of rats were treated orally, by gavage, with single doses of 1,2-dichloropropane ranging from 55 to 400 mg/kg body weight. 1,2-Dichloropropane was no longer detectable in the blood 24 h after dosing at any dose level (Di Nucci et al., 1988). （P33）