and Shirasu, Y. (1984). Potential toxicity of 2-*sec*-Butyl Methylcarbamate (BPMC) by *O,O*-Dimethyl *O*-(3-Methyl-4-nitrophenyl)phosphorothioate (Fenthion) in mice; relationship between acute toxicity and metabolism of BPMC. Fundaml. Appl. Toxicol. 4, 718-723.

13) Miyaoka, T., Takahashi, H., Tsuda, S., and Shirasu, Y. (1984). Potentiation of acute toxicity of 2-*sec*-Butyl Methylcarbamate (BPMC) by Fenthion in mice. Fundaml. Appl. Toxicol. 4, 802-807.

14) Mileson, B. E., Chambers, J. E., Chen, W. L., Dettbarn, W., Ehrich, M., Eldefrawi, A. T., Gaylor, D. W., Hamerink, K., Hodgson, E., Karczmar, A. G., Padilla, S., Pope, C. N., Richardoson, R. J., Saunders, D. R., Sheets, L. P., Sultatos, L. G., and Wallace, K. B.(1998). Common mechanism of Toxicity: a case study of organophosphorus pesticides. Toxicol. Sci. 41, 8-20.

15) Hrdina, P. D., Singhal, R. L., Peters, D. A. V., and Ling, G. M. (1973). Some neurochemical alterations during acute DDT poisoning. Toxicol. Appl. Pharmacol. 25, 276-288.

16) Carlock, L. L., Che, W. L., Gardon, E. B., Killeen, J. C., Manley, A., Meyer, L. S., Pendino, K. J., Percy, A., Sargent D. E., Seaman L. R., Suanborg, N. S., Stanton, R. H., Tellone, C. I., and Van Goethem, D. L. (1999). Regulating and assessing risks of cholinesterace-inhibiting pesticides: divergent approaches and interpretations. J. Toxicol. Environ. Health B Crit. Rev. 2, 105-160.

17) Lotti M. (1995). Cholinesterace inhibition: complexities in interpretation. Clin. Chem. 41, 1814-1818.

18) Bignami, G., Rosic, N., Michalek, H., Milosevic, M., and Gatti, G. L. (1975). Behavioral toxicity of anticholinesterase agents. Methodological, neurochemical, and neuropsychological aspects. In: Weise, B., and Laties, V. G. (eds.), Behavioral Toxicology. Plenum Press, NY, USA, 155-216

19) Padilla, S., Moser, V. C., Pope, C. N., and Brimijoin, W. S. (1992). Paraoxon toxicity is not potentiated by prior reduction in blood acetylcholinesterase. Toxicol. Appl. Pharmacol. 117, 110-115.

20) Moser, V. C. (1999). Comparison of aldicarb and methamidophos neurotoxicity at different ages in the rat: behavioral and biochemical parameters. Toxicol. Appl. Pharmacol. 157, 94-106.

21) Hingtgen J. N. and Aprison M. H. (1976). Behavioral and environmental aspects of the cholinergic system. In: Goldberg, A. M. and Hanin, I. (eds.), Biology of cholinergic function. Raven Press, NY, USA, 515-559.

G. 研究発表

1. 論文発表

なし

2. 学会発表

なし

H. 知的財産権の出願・取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Table 1 Mortality and clinical signs in female rats

Group	Signs	1 hour	4 hours	1 day	2-7 days
Control	Mortality	0/24[a]	0/24	0/24	0/12
	Twitches	0/24	0/24	0/24	0/12
	Tremor	0/24	0/24	0/24	0/12
	Miosis	0/24	0/24	0/24	0/12
	Salivation	0/24	0/24	0/24	0/12
	Lacrimation	0/24	0/24	0/24	0/12
MPP	Mortality	0/12	0/12	0/12	0/6
	Twitches	0/12	0/12	0/12	0/6
	Tremor	0/12	0/12	0/12	0/6
	Miosis	9/12 **	12/12 **	0/12	0/6
	Salivation	0/12	0/12	0/12	0/6
	Lacrimation	0/12	0/12	0/12	0/6
DDT	Mortality	0/12	0/12	0/12	0/6
	Twitches	0/12	0/12	0/12	0/6
	Tremor	0/12	0/12	0/12	0/6
	Miosis	0/12	0/12	0/12	0/6
	Salivation	0/12	0/12	0/12	0/6
	Lacrimation	0/12	0/12	0/12	0/6
MPMC	Mortality	0/12	0/12	0/12	0/6
	Twitches	12/12 **	0/12	0/12	0/6
	Tremor	7/12 **	0/12	0/12	0/6
	Miosis	12/12 **	8/12 **	0/12	0/6
	Salivation	10/12 **	0/12	0/12	0/6
	Lacrimation	10/12 **	0/12	0/12	0/6
MPP + MPP	Mortality	0/12	0/12	0/12	0/6
	Twitches	0/12	12/12 **	0/12	0/6
	Tremor	0/12	0/12	0/12	0/6
	Miosis	11/12 **	12/12 **	0/12	0/6
	Salivation	0/12	0/12	0/12	0/6
	Lacrimation	0/12	0/12	0/12	0/6
MPP + DDT	Mortality	0/12	0/12	0/12	0/6
	Twitches	0/12	0/12	0/12	0/6
	Tremor	0/12	0/12	0/12	0/6
	Miosis	12/12 **	12/12 **	1/12	0/6
	Salivation	0/12	0/12	0/12	0/6
	Lacrimation	0/12	0/12	0/12	0/6
MPP + MPMC	Mortality	4/12 **	0/8	0/8	0/4
	Twitches	8/8 **	8/8 **	1/8	0/4
	Tremor	3/8 *	6/8 **	0/8	0/4
	Miosis	8/8 **	8/8 **	2/8	0/4
	Salivation	8/8 **	5/8 **	0/8	0/4
	Lacrimation	7/8 **	2/8	0/8	0/4

a ; Number of animals noted / number of animals examined.
Significantly different from control: *, $p <= 0.05$; **, $p<=0.01$ (Fisher's exact probability test).

Table 2-1 Motor activity in female rats - 1 day after treatment

Group		Counts/10 min. 0-10	10-20	20-30	30-40	40-50	50-60	Total
Control	mean	1144	364	130	68	73	122	1901
	S.D.	393	356	196	124	102	212	989
MPP	mean	1247	701	333	411 *	407 *	233	3332 *
	S.D.	321	378	297	472	434	237	1581
DDT	mean	1139	531	257	263	300 **	492 *	2982 *
	S.D.	237	196	320	278	215	435	678
MPMC	mean	1201	243	126	159	235	19	1983
	S.D.	186	224	124	247	305	38	870
MPP + MPP	mean	1277	534	362	201	38	263	2676
	S.D.	314	346	420	231	42	261	1120
MPP + DDT	mean	1056	288	207	118	130	152	1951
	S.D.	557	181	302	110	196	296	1048
MPP + MPMC	mean	630 *	194	43	52	63	60	1042
	S.D.	415	248	86	52	64	101	1042

S.D.: Standard deviation.
Significantly different from control: *, p <= 0.05; **, p<=0.01 (Student *t*-test).

Table 2-2 Motor activity in female rats - 7 days after treatment

Group		Counts/10 min. 0-10	10-20	20-30	30-40	40-50	50-60	Total
Control	mean	1138	400	252	116	102	97	2104
	S.D.	475	315	252	172	140	189	786
MPP	mean	1334	727	437	221	256	108	3083
	S.D.	264	456	308	221	297	82	1088
DDT	mean	1495	228	346	218	23	389	2699
	S.D.	1773	307	317	306	27	467	1006
MPMC	mean	1418	902 *	289	448 **	102	239	3398 **
	S.D.	340	494	244	302	159	387	1415
MPP + MPP	mean	862	344	163	257	59	8	1693
	S.D.	411	312	189	174	69	18	833
MPP + DDT	mean	1732 *	911 *	439	220	115	292	3707 **
	S.D.	322	512	365	253	205	337	407
MPP + MPMC	mean	1445	778	456	573 *	460	284	3996
	S.D.	374	644	337	658	897	530	3319

S.D.: Standard deviation.
Significantly different from control: *, p <= 0.05; **, p<=0.01 (Student *t*-test).

Table 3 Cholinesterase activity in female rats

Group			Plasma (U/L)		Erythrocyte (U/mL)		Brain (U/L)	
Control	1 day after treatment	mean	2399		0.33		419	
		S.D.	587		0.04		41	
	7 days after treatment	mean	2425		0.34		439	
		S.D.	579		0.03		38	
MPP	1 day after treatment	mean / Sig.	309	**	0.13	**	237	**
		S.D. / Ratio	105	13%	0.04	39%	30	57%
	7 days after treatment	mean / Sig.	2376		0.25	**	365	**
		S.D. / Ratio	811	98%	0.03	74%	29	83%
DDT	1 day after treatment	mean / Sig.	1742		0.31		443	
		S.D. / Ratio	689	73%	0.01	94%	21	106%
	7 days after treatment	mean / Sig.	2156		0.29	*	440	
		S.D. / Ratio	685	89%	0.05	85%	36	100%
MPMC	1 day after treatment	mean / Sig.	1914		0.29	*	447	
		S.D. / Ratio	463	80%	0.02	88%	27	107%
	7 days after treatment	mean / Sig.	2426		0.31		428	
		S.D. / Ratio	612	100%	0.03	91%	14	97%
MPP + MPP	1 day after treatment	mean / Sig.	239	**	0.09	**	207	**
		S.D. / Ratio	62	10%	0.03	27%	34	49%
	7 days after treatment	mean / Sig.	2218		0.21	**	342	**
		S.D. / Ratio	506	91%	0.02	62%	22	78%
MPP + DDT	1 day after treatment	mean / Sig.	225	**	0.12	**	217	**
		S.D. / Ratio	48	9%	0.03	36%	26	52%
	7 days after treatment	mean / Sig.	2210		0.23		348	**
		S.D. / Ratio	470	91%	0.02	68%	29	79%
MPP + MPMC	1 day after treatment	mean / Sig.	256	**	0.17	**	251	**
		S.D. / Ratio	103	11%	0.08	52%	43	60%
	7 days after treatment	mean / Sig.	1725	*	0.26	**	374	**
		S.D. / Ratio	431	71%	0.04	76%	18	85%

S.D.: Standard deviation.
Significantly different from control: *, p <= 0.05; **, p<=0.01 (Student *t*-test).
Ratio: Percentage to the control value.

別添４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
M. Murata, S. Ohnishi, K. Seike, K. Fukuhara, N. Miyata, and S. Kawanishi.	Oxidative DNA damage induced by carcinogenic dinitropyrenes in the presence of P450 reductase.	Chem. Res. Toxicol.	17	1750-1756	2004
K. Sakano, Y. Inagaki, S. Oikawa, Y. Hiraku, and S. Kawanishi.	Copper-mediated oxidative DNA damage induced by eugenol: possible involvement of *O*-demethylation.	Mutat. Res.	565	35-44	2004
K. Seike, M. Murata, K. Hirakawa, Y. Deyashiki, and S. Kawanishi.	Oxidative DNA damage induced by benz[a]anthracene dihydrodiols in the presence of dihydrodiol dehydrogenase.	Chem. Res. Toxicol.	17	1445-1451	2004
Y. Hiraku, A. Sekine, H. Nabeshi, K. Midorikawa, M. Murata, Y. Kumagai, and S. Kawanishi.	Mechanism of carcinogenesis induced by a veterinary antimicrobial drug, nitrofurazone, via oxidative DNA damage and cell proliferation.	Cancer Lett.	215	141-150	2004
H. Kobayashi, S. Oikawa, K. Hirakawa, and S. Kawanishi.	Metal-mediated oxidative damage to cellular and isolated DNA by gallic acid, a metabolite of antioxidant propyl gallate.	Mutat. Res.	558	111-120	2004
M. Murata, K. Midorikawa, M. Koh, K. Umezawa, and S. Kawanishi.	Genistein and daidzein induce cell proliferation and their metabolites cause oxidative DNA damage in relation to isoflavone-induced cancer of	Biochemistry	43	2569-2577	2004

	estrogen-sensitive organs.				
T. Takada, M. Ogino, M. Miyata, K, Nagata and Y. Yamazoe.	Diffreneces in transactivation between rat CYP3A1 and human CYP3A4 gens by human pregnane X receptor.	Drug Metab. Pharmacokin.	19	103-113	2004
M. Miyata, H. Takano, L.Q. Guo, K. Nagata and Y. Yamazoe.	Grapefruit juice intake does not enhance but rather protects against aflatoxin B1-induced liver DNA damage through a reduction in hepatic CYP3A activity.	Carcinogenesis	25	203-220	2004
T. Matsubara, H.J. Kim, M. Miyata, M. Shimada, K. Nagata and Y. Yamazoe.	Isolation and characterization of a new major intestinal CYP3A form, CYP3A62, in rat.	J. Pharmacol. Exp. Ther.	309	1282-1290	2004
M. Shimada, R. Terazawa, Y. Kamiyama, W. Honma, K. Nagata and Y. Yamazoe.	Unique properties of a renal sulfotransferase, Stld1 in dopamine metabolism.	J. Pharmacol. Exp. Ther.	310	808-814	2004
T. Shiraga, T. Niwa, Y. Ohno, A. Kagayama.	Interindividual variability in 2-hydroxylation, 3-sulfation, and 3-glucuronidation of ethynylestradiol in human liver.	Biol. Pharm. Bull.	27	1900-1906	2004
Kuribayashi, M., Asamoto, M., Suzuki, S., Hokaiwado, N., Ogawa, K., Shirai, T.	Lack of modification of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) rat hepatocarcinogenesis by caffeine, a CYP1A2 inducer, points to complex counteracting influence.	Cancer Lett.		In press	2005