Table 1 Results of reverse mutation test (I) of 4-chloro-*o*-cresol on bacteria

With (+) or Without (-) S9 mix	Test Substance Concentration (μg/plate)	Number of revertants (number of colonies / plate)				
		Base-pair change type			Frameshift type	
		TA100	TA1535	WP2 *uvrA*	TA98	TA1537
S9 mix (-)	0	86 75 (84) 90 (± 8)	11 7 (9) 8 (± 2)	30 27 (33) 42 (± 8)	12 22 (16) 15 (± 5)	3 7 (6) 8 (± 3)
	19.5	71 79 (77) 81 (± 5)	7 11 (7) 4 (± 4)		14 9 (13) 16 (± 4)	3 3 (3) 4 (± 1)
	39.1	84 81 (79) 71 (± 7)	11 7 (9) 10 (± 2)	28 36 (35) 41 (± 7)	18 18 (16) 11 (± 4)	2 9 (5) 5 (± 4)
	78.1	79 92 (85) 85 (± 7)	3 7 (6) 8 (± 3)	33 39 (38) 43 (± 5)	24 12 (16) 12 (± 7)	4 7 (6) 6 (± 2)
	156	75 83 (83) 91 (± 8)	16 7 (10) 8 (± 5)	25 27 (29) 36 (± 6)	9 15 (13) 15 (± 3)	5 3 (5) 7 (± 2)
	313	66 68 (65) 61 (± 4)	13 7 (10) 10 (± 3)	28 31 (31) 33 (± 3)	9 11 (9) 7 (± 2)	6 6 (5) 4 (± 1)
	625	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	12* 4* (8) 7* (± 4)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)
	1250			0* 0* (0) 0* (± 0)		
S9 mix (+)	0	84 74 (84) 95 (± 11)	9 9 (10) 11 (± 1)	28 28 (33) 42 (± 8)	24 28 (22) 15 (± 7)	13 8 (10) 8 (± 3)
	39.1	102 85 (92) 89 (± 9)	7 8 (8) 10 (± 2)	53 28 (39) 35 (± 13)	14 20 (21) 28 (± 7)	3 7 (5) 6 (± 2)
	78.1	103 95 (104) 115 (± 10)	9 6 (7) 7 (± 2)	36 45 (35) 25 (± 10)	19 19 (18) 17 (± 1)	9 11 (8) 4 (± 4)
	156	86 91 (91) 96 (± 5)	13 5 (9) 10 (± 4)	39 22 (36) 47 (± 13)	27 21 (25) 26 (± 3)	7 10 (8) 7 (± 2)
	313	76 96 (88) 92 (± 11)	10 14 (11) 9 (± 3)	36 43 (39) 37 (± 4)	27 15 (20) 19 (± 6)	11 4 (6) 4 (± 4)
	625	53* 41* (41) 30* (± 12)	6 8 (6) 5 (± 2)	27 26 (26) 25 (± 1)	21* 10* (15) 13* (± 6)	4* 2* (3) 2* (± 1)
	1250	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)
Positive control	Name	AF-2	NaN_3	ENNG	AF-2	9-AA
	Concentration (μg/plate)	0.01	0.5	2	0.1	80
S9 mix (-)	Number of revertants	508 411 (455) 446 (± 49)	307 264 (293) 307 (± 25)	467 471 (491) 536 (± 39)	426 472 (449) 448 (± 23)	814 716 (753) 729 (± 53)
Positive control	Name	2-AA	2-AA	2-AA	2-AA	2-AA
	Concentration (μg/plate)	1	2	10	0.5	2
S9 mix (+)	Number of revertants	893 829 (838) 792 (± 51)	316 312 (304) 283 (± 18)	764 788 (784) 799 (± 18)	334 387 (364) 371 (± 27)	173 155 (159) 150 (± 12)

AF-2: 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, NaN_3: sodium azide (Mean)
ENNG: N-ethyl-N'-nitro-N-nitrosoguanidine, 9-AA: 9-aminoacridine, 2-AA: 2-aminoanthracene (±S.D.)

*: Microbial toxicity was observed.

Table 2 Results of reverse mutation test (II) of 4-chloro-*o*-cresol on bacteria

With (+) or Without (-) S9 mix	Test Substance Concentration (μg/plate)	Number of revertants (number of colonies / plate)				
		Base-pair change type			Frameshift type	
		TA100	TA1535	WP2 *uvrA*	TA98	TA1537
S9 mix (-)	0	87 77 (80) 76 (± 6)	13 9 (11) 12 (± 2)	20 32 (26) 25 (± 6)	9 11 (11) 14 (± 3)	3 4 (5) 7 (± 2)
	19.5	73 80 (75) 73 (± 4)	7 9 (8) 8 (± 1)		16 12 (14) 14 (± 2)	4 3 (4) 5 (± 1)
	39.1	80 77 (79) 80 (± 2)	11 13 (11) 8 (± 3)	29 17 (27) 36 (± 10)	15 15 (14) 13 (± 1)	3 3 (3) 2 (± 1)
	78.1	85 81 (78) 69 (± 8)	10 9 (9) 8 (± 1)	18 26 (21) 19 (± 4)	13 21 (14) 8 (± 7)	6 9 (6) 2 (± 4)
	156	74 76 (78) 85 (± 6)	10 9 (8) 6 (± 2)	28 25 (25) 21 (± 4)	13 15 (13) 11 (± 2)	4 2 (4) 5 (± 2)
	313	72 79 (73) 68 (±6)	10 8 (9) 9 (± 1)	22 23 (21) 19 (± 2)	8 10 (9) 9 (± 1)	4 7 (5) 4 (± 2)
	625	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	10* 5* (6) 4* (± 3)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)
	1250			0* 0* (0) 0* (± 0)		
S9 mix (+)	0	84 84 (85) 86 (± 1)	15 11 (12) 9 (± 3)	23 26 (25) 25 (± 2)	17 17 (20) 26 (± 5)	8 8 (7) 4 (± 2)
	39.1	83 86 (90) 101 (± 10)	10 9 (9) 8 (± 1)	36 28 (30) 25 (± 6)	16 19 (18) 20 (± 2)	5 10 (6) 3 (± 4)
	78.1	95 92 (97) 103 (± 6)	9 9 (8) 7 (± 1)	32 24 (31) 37 (± 7)	20 33 (26) 24 (± 7)	4 6 (6) 8 (± 2)
	156	97 92 (93) 91 (± 3)	8 15 (10) 8 (± 4)	32 25 (26) 21 (± 6)	26 16 (19) 14 (± 6)	11 9 (11) 12 (± 2)
	313	112 96 (106) 109 (± 9)	9 8 (8) 7 (± 1)	28 35 (30) 28 (± 4)	20 18 (22) 27 (± 5)	10 6 (8) 8 (± 2)
	625	13* 13* (12) 9* (± 2)	2* 1* (2) 2* (± 1)	27 12 (19) 17 (± 8)	4* 4* (3) 2* (± 1)	0* 0* (0) 0* (± 0)
	1250	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)	0* 0* (0) 0* (± 0)
Positive control	Name	AF-2	NaN_3	ENNG	AF-2	9-AA
	Concentration (μg/plate)	0.01	0.5	2	0.1	80
S9 mix (-)	Number of revertants	578 513 (535) 513 (± 38)	326 352 (344) 353 (± 15)	539 519 (510) 473 (± 34)	460 390 (417) 402 (± 37)	467 501 (456) 399 (± 52)
Positive control	Name	2-AA	2-AA	2-AA	2-AA	2-AA
	Concentration (μg/plate)	1	2	10	0.5	2
S9 mix (+)	Number of revertants	1088 1098 (1048) 959 (± 78)	424 450 (454) 488 (± 32)	647 712 (704) 753 (± 53)	388 334 (374) 401 (± 36)	161 154 (152) 140 (± 11)

AF-2: 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, NaN_3: sodium azide (Mean)
ENNG: *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine, 9-AA: 9-aminoacridine, 2-AA: 2-aminoanthracene – (±S.D.)

*: Microbial toxicity was observed.

4-クロロ-o-クレゾールの
チャイニーズ・ハムスター培養細胞を用いる染色体異常試験

In Vitro Chromosomal Aberration Test of 4-Chloro-o-cresol on Cultured Chinese Hamster Cells

要約

OECD既存化学物質安全性点検に係わる毒性調査事業の一環として，4-クロロ-o-クレゾールの培養細胞に及ぼす細胞遺伝学的影響を評価するため，チャイニーズ・ハムスター培養細胞（CHL/IU，以下CHLと略す）を用いて試験管内染色体異常試験を実施した．

染色体異常試験に用いる濃度を決定するため，細胞増殖抑制試験を行ったところ，連続処理法の24時間処理および48時間処理において約50%の増殖抑制を示す濃度は，それぞれ0.053，0.017 mg/ml，短時間処理法のS9 mix存在下および非存在下では，それぞれ0.072，0.121 mg/mlであった．従って染色体異常試験において，連続処理法の24時間処理では0.060 mg/ml，48時間処理では0.020 mg/ml，短時間処理法のS9 mix存在下では0.080 mg/ml，非存在下では0.125 mg/mlを高濃度とし，それぞれその1/2の濃度を中濃度，1/4の濃度を低濃度に設定した．

CHL細胞を被験物質で24時間および48時間連続処理した結果，いずれの処理群においても，染色体の構造異常や倍数性細胞の出現頻度は5%未満であった．また，短時間処理法のS9 mix存在下および非存在下のいずれの処理群においても，倍数性細胞の出現頻度は5%未満であった．しかし，短時間処理法のS9 mix存在下の高濃度群(0.080 mg/ml)で，観察した細胞の7.5%に染色体構造異常が誘発され，判定は疑陽性であった．従って，再現性を確認するため，0.040，0.080，0.120 mg/mlの濃度で確認試験を実施した．その結果，0.080，0.120 mg/mlで観察した細胞のそれぞれ7.0，21.0%に染色体構造異常が観察され，染色体異常誘発の再現性が確認されると共に構造異常細胞の明らかな増加が認められたため，短時間処理法のS9 mix存在下で陽性と判定した．

以上の結果より4-クロロ-o-クレゾールは，上記の試験条件下で，試験管内のCHL細胞に染色体異常を誘発すると結論した．

材料および方法

1. 使用した細胞

大日本製薬㈱から入手(1994年8月，入手時：継代14代)したチャイニーズ・ハムスター由来のCHL細胞を，解凍後継代5代以内で試験に用いた．

2. 培養液の調製

培養には，仔牛血清(CS:GIBCO LABORATORIES，ロット番号:43N1140)を10%添加したイーグルMEM培養液を用いた．

3. 培養条件

2×10^4個のCHL細胞を，培養液5mlを入れたディシュ(径6cm，Becton Dickinson and Company)に播き，37℃のCO_2インキュベーター(5%CO_2)内で培養した．

連続処理法では，細胞播種3日目に被験物質を加え，24時間および48時間処理した．また，短時間処理法では，細胞播種3日目にS9 mixの存在下および非存在下で6時間処理し，処理終了後新鮮な培養液でさらに18時間培養した．

4. 被験物質

4-クロロ-o-クレゾール(CAS No.:1570-64-5，ロット番号:FBY01，純度:93.9%;東京化成工業㈱)は，分子量142.58，融点40℃，沸点220～225℃の白色結晶塊で通常の取り扱い条件では安定である．なお，本ロットについては試験期間中安定であることを確認した．

5. 被験物質溶液の調製

被験物質調製液は，用時調製した．溶媒はジメチルスルホキシド(DMSOと略す．関東化学㈱，ロット番号:603E2089)を用いた．原体を溶媒に溶解して原液を調製し，ついで原液を溶媒で順次希釈して所定の濃度の被験物質調製液を作製した．また，調製に際しては純度換算(93.9%)を実施した．被験物質調製液は，すべての試験において培養液の0.5(v/v)%になるように加えた．染色体異常試験に用いた最高および最低濃度の被験物質調製液について濃度分析を実施し，いずれも所定濃度の100±5%以内であることを確認した．

6. 細胞増殖抑制試験による処理濃度の決定

染色体異常試験に用いる被験物質の処理濃度を決定するため，被験物質の細胞増殖に及ぼす影響を調べた．被験物質のCHL細胞に対する増殖抑制作用は，血球計算盤を用いて各群の生存細胞を数え，陰性対照群に対する細胞増殖の比をもって指標とした．

その結果，4-クロロ-o-クレゾールの約50%の増殖抑制を示す濃度を，50%をはさむ2濃度の値より算出したところ，連続処理法の24時間処理および48時間処理ではそれぞれ0.053，0.017 mg/ml，短時間処理法のS9 mix存在下および非存在下ではそれぞれ0.072，0.121 mg/mlであった(Fig. 1)．

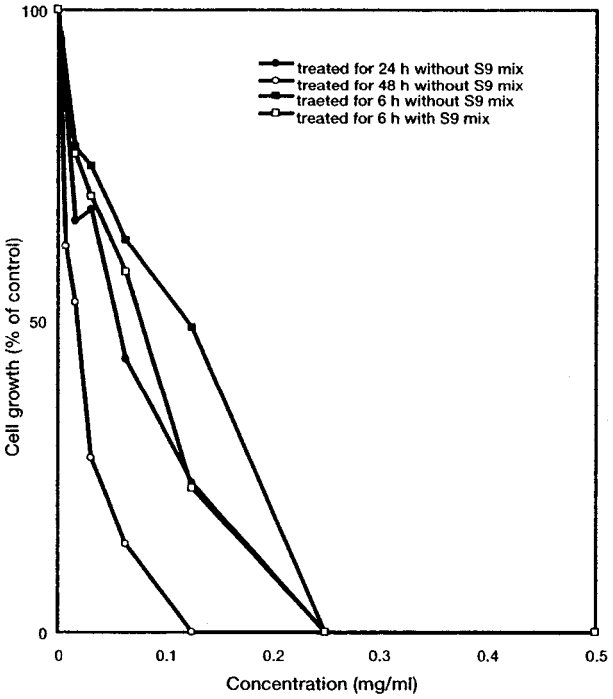

Fig. 1 Inhibition of cell growth treated with 4-chloro-*o*-cresol

7. 実験群の設定

細胞増殖抑制試験の結果より，染色体異常試験で用いる被験物質の高濃度群を連続処理法の24時間処理では0.060 mg/m*l*，48時間処理では0.020 mg/m*l*，短時間処理法のS9 mix存在下では0.080 mg/m*l*，非存在下では0.125 mg/m*l*を高濃度とし，それぞれその1/2の濃度を中濃度，1/4の濃度を低濃度として設定した．

8. 染色体標本作製法

培養終了の2時間前に，コルセミドを最終濃度が約0.1 μg/m*l*になるように培養液に加えた．染色体標本の作製は常法に従って行った．スライド標本は各シャーレにつき2枚作製した．作製した標本を，3%ギムザ溶液で20分間染色した．

9. 染色体分析

作製したスライド標本のうち，1枚のシャーレから得られたスライドを処理条件が分からないようにコード化した状態で分析した．染色体の分析は，日本環境変異原学会・哺乳動物試験分科会(MMS)[1]による分類法に基づいて行い，染色体型あるいは染色分体型のギャップ，切断，交換などの構造異常の有無と倍数性細胞(polyploid)の有無について観察した．また，構造異常および倍数性細胞については1群200個の分裂中期細胞を分析した．

10. 記録と測定

溶媒および陽性対照群と被験物質処理群についての分析結果は，観察した細胞数，構造異常の種類と数，倍数性細胞の数について集計し，各群の値を記録用紙に記入した．被験物質の染色体異常誘発性についての判定は，石館ら[2]の判定基準に従い，染色体異常を有する細胞の頻度が5%未満を陰性，5%以上10%未満を疑陽性，10%以上を陽性とした．

結果および考察

連続処理法による染色体分析の結果をTable 1に示した．4-クロロ-*o*-クレゾールを加えて，24時間および48時間処理した各濃度群で，染色体の構造異常および倍数性細胞の出現頻度は5%未満であった．

短時間処理法による染色体分析の結果をTable 2に示した．4-クロロ-*o*-クレゾールを加えてS9 mix存在下および非存在下で6時間処理した各濃度群で，倍数性細胞の出現頻度は5%未満であった．また，短時間処理法のS9 mix存在下の高濃度群(0.080 mg/m*l*)で，観察した細胞の7.5%に染色体構造異常(gapを含む)が誘発され，判定は疑陽性であった．

従って，再現性を確認するため，0.040，0.080，0.120 mg/m*l*の濃度で確認試験を実施した(Table 3)．その結果，0.080，0.120 mg/m*l*で観察した細胞のそれぞれ7.0，21.0%に染色体構造異常が観察され，染色体異常誘発性の再現性が確認されると共に構造異常細胞の明らかな増加が認められたため，短時間処理法のS9 mix存在下で陽性と判定した．

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Table 1 Chromosomal analysis of Chinese hamster cells (CHL) continuously treated with 4-chloro-*o*-cresol without S9 mix (main test)

Group	Concentration (mg/ml)	Time of exposure (h)	No. of cells analysed	No. of structural aberrations							No. of cells with aberrations		Polyploid[2] (%)	Judgement[3]	
				gap	ctb	cte	csb	cse	f	total	-g (%)	+g (%)		SA	NA
Solvent[1]	0	24	200	1	1	0	2	0	0	4	3 (1.5)	4 (2.0)	0.0		
C-*o*-C	0.015	24	200	0	3	0	1	0	0	4	4 (2.0)	4 (2.0)	0.0	-	-
	0.030	24	200	2	7	0	0	0	0	9	7 (3.5)	9 (4.5)	0.5	-	-
	0.060	24	200	0	9	0	0	0	0	9	9 (4.5)	9 (4.5)	0.0	-	-
MC	0.00003	24	200	0	24	11	3	0	0	38	37 (18.5)	37 (18.5)	0.0	+	-
Solvent	0	48	200	0	2	0	0	0	0	2	2 (1.0)	2 (1.0)	0.0		
C-*o*-C	0.005	48	200	0	0	0	1	0	0	1	1 (0.5)	1 (0.5)	0.0	-	-
	0.010	48	200	0	2	1	0	0	0	3	3 (1.5)	3 (1.5)	0.5	-	-
	0.020	48	200	0	6	1	1	0	0	8	8 (4.0)	8 (4.0)	0.0	-	-
MC	0.00003	48	200	0	24	34	8	0	0	66	56 (28.0)	56 (28.0)	0.0	+	-

Abberviations : gap : chromatid gap and chromosome gap, ctb : chromatid break, cte : chromatid exchange, csb : chromosome break, cse : chromosome exchange (dicentric and ring etc.), f : acentric fragment (chromatid type), -g : total no. cells with aberrations except gap, +g : total no. of cells with aberrations, SA : structural aberration, NA : numerical aberration, C-*o*-C : 4-chloro-*o*-cresol, MC : mitomycin C
1) Dimethylsulfoxide was used as solvent. 2) Two hundred cells were analysed in each group. 3) Judgement was done on the basis of the criteria of Ishidate et al.(1987).

Table 2 Chromosomal analysis of Chinese hamster cells (CHL) treated with 4-chloro-*o*-cresol with and without S9 mix (main test)

Group	Concentration (mg/ml)	S9 mix	Time of exposure (h)	No. of cells analysed	No. of structural aberrations							No. of cells with aberrations		Polyploid[2] (%)	Judgement[3]	
					gap	ctb	cte	csb	cse	f	total	-g (%)	+g (%)		SA	NA
Solvent[1]	0	-	6-(18)	200	0	1	0	0	0	0	1	1 (0.5)	1 (0.5)	0.0		
C-*o*-C	0.0313	-	6-(18)	200	0	2	0	1	0	0	3	3 (1.5)	3 (1.5)	1.0	-	-
	0.0625	-	6-(18)	200	1	0	0	1	0	0	2	1 (0.5)	2 (1.0)	1.0	-	-
	0.125	-	6-(18)	200	1	3	3	0	0	0	7	6 (3.0)	7 (3.5)	1.5	-	-
BP	0.020	-	6-(18)	200	0	0	0	1	0	0	1	1 (0.5)	1 (0.5)	0.0	-	-
Solvent	0	+	6-(18)	200	0	1	0	0	0	0	1	1 (0.5)	1 (0.5)	0.5		
C-o-C	0.020	+	6-(18)	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0	-	-
	0.040	+	6-(18)	200	1	1	0	1	0	0	3	2 (1.0)	3 (1.5)	0.5	-	-
	0.080	+	6-(18)	200	0	7	10	0	0	0	17	15 (7.5)	15 (7.5)	1.0	±	-
BP	0.020	+	6-(18)	200	2	69	118	1	0	0	190	132 (66.0)	133 (66.5)	1.5	+	-

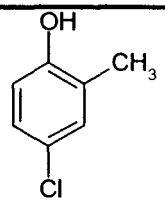
Abberviations : gap : chromatid gap and chromosome gap, ctb : chromatid break, cte : chromatid exchange, csb : chromosome break, cse : chromosome exchange (dicentric and ring etc.), f : acentric fragment (chromatid type), -g : total no. cells with aberrations except gap, +g : total no. of cells with aberrations, SA : structural aberration, NA : numerical aberration, C-*o*-C : 4-chloro-*o*-cresol, BP : benzo[a]pyrene
1) Dimethylsulfoxide was used as solvent. 2) Two hundred cells were analysed in each group. 3) Judgement was done on the basis of the criteria of Ishidate et al.(1987).

Table 3 Chromosomal analysis of Chinese hamster cells (CHL) treated with 4-chloro-*o*-cresol with S9 mix (confirmation test)

Group	Concentration (mg/ml)	S9 mix	Time of exposure (h)	No. of cells analysed	No. of structrual aberrations							No. of cells with aberrations		Polyploid[2] (%)	Judgement[3]	
					gap	ctb	cte	csb	cse	f	total	-g (%)	+g (%)		SA	NA
Solvent[1]	0	+	6-(18)	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.0		
C-*o*-C	0.040	+	6-(18)	200	1	5	4	0	0	0	10	6 (3.0)	7 (3.5)	1.0	-	-
	0.080	+	6-(18)	200	1	5	11	1	0	0	18	13 (6.5)	14 (7.0)	1.5	±	-
	0.120	+	6-(18)	200	0	24	28	1	0	0	53	42 (21.0)	42 (21.0)	0.5	+	-
BP	0.020	+	6-(18)	200	1	70	143	1	3	0	218	149 (74.5)	149 (74.5)	0.0	+	-

Abberviations : gap : chromatid gap and chromosome gap, ctb : chromatid break, cte : chromatid exchange, csb : chromosome break, cse : chromosome exchange (dicentric and ring etc.), f : acentric fragment (chromatid type), -g : total no. cells with aberrations except gap, +g : total no. of cells with aberrations, SA : structural aberration, NA : numerical aberration, C-*o*-C : 4-chloro-*o*-cresol, BP : benzo[a]pyrene
1) Dimethylsulfoxide was used as solvent. 2) Two hundred cells were analysed in each group. 3) Judgement was done on the basis of the criteria of Ishidate et al.(1987).

SIDS INITIAL ASSESSMENT PROFILE

CAS Nr.	1570-64-5
Chemical Name	Phenol, 4-chloro-2-methyl
Structural formula	

CONCLUSIONS AND RECOMMENDATIONS

Environment

The chemical is very toxic to aquatic organisms. The chemical is considered as readily biodegradable and has a low bioaccumulative potential. The predicted environmental concentrations are lower than the predicted no effect levels for all environmental compartments. It is currently considered of low potential risk and low priority for further work.

Health

This chemical is corrosive and toxic by inhalation. Workers exposure is considered to be low because the substance is produced in a closed system as an intermediate for the manufacturing of phenoxyherbicides. Consumer exposure is considered to be negligible. It is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The EU tonnage of (4-chloro-2-methylphenol) for the year 1989 has been estimated as a total of 15000 tons per annum based on the production volumes presented by the manufacturers and supported by the production and consumption figures of the herbicides MCPA (4-chloro-2-methylphenoxy acetic acid), MCPB (4-chloro-2-methylphenoxy butyric acid) and MCPP (mecoprop 2-4chloro-2-methylphenoxy-propionic acid). The main points of emissions are at manufacturing sites of the substance where PCOC is used as an intermediate for manufacturing of the phenoxyherbicides (i.e. PCOC processing and phenoxyherbicides formulation sites) and where these herbicides are used in agriculture (PCOC occurs as an impurity in the phenoxyherbicides). The environmental distribution of PCOC (using a Mackay fugacity level 1 calculation (Mackay & Paterson 1990) is expected to be 33% in air, 56% in water, 6% in soil and 5% in sediment.

The environmental exposure assessment is primarily based on monitoring data from the two main manufacturing sites in EU where all production and all processing of PCOC takes place, and where approximately 60% of the production volume in EU is formulated. A worst case environmental exposure scenario for a separate, but hypothetical, formulation site has also been considered. PEC local water is calculated as 0.0038 mg/l and 0.0014 mg/l for specific site and formulation, respectively. For the exposure assessment of PCOC in sewerage treatment plants (STP), the dissolved concentration of PCOC is assumed to be equal to the effluent concentration. The predicted environment concentrations for the sewerage treatment plant are: 0.004 mg/l [specific

site], 0.0013 mg/l [formulation]. The predicted environmental concentration for soil is calculated as 0.00000088 - 0.000002 mg/kg.

PCOC is very toxic to aquatic organisms. The acute toxicity to fish LC_{50} (96h) was observed to be 2.3-6.6mg/l. The EC_{50} (48h) to daphnids was 0.29-1.0 mg/l and the EC_{50} (96h) to algae was 8.2 mg/l and EC_{10} to algae (96h) was 0.89 mg/l. The NOEC (28 days) for fish was 0.5 mg/l for histopathological changes in kidneys and liver. NOEC (21 days) for Daphnia reproduction was 0.55 mg/l. The presence of an algae EC_{10}, a long term NOEC for fish and a Daphnia reproduction test suggest that use of an assessment factor of 10 may be appropriate. The predicted no effect concentration (PNEC) is 0.05 mg/l. The PNEC $STP_{microrgnaisms}$ is obtained by using the EC50 for inhibition of respiration of activated sludge microorganisms and an assessment factor of 100 (0.55 mg/l). Since no ecotoxicological data are available for soil organisms the equilibrium partitioning method has been applied ($PNEC_{soil}$ = 0.36 mg/kg).

A local risk for aquatic organisms is not anticipated as the predicted environment concentration is lower than the predicted no effect concentration(regardless of whether an assessment factor of 10 or 100 is employed). Similarly the risks for microorganisms in sewerage treatment plants and for soil organisms is not expected.

The most important sources of direct human exposure are assumed to be at production sites (with predicted exposures of up to 0.7 mg/kg/day) or in conjunction with the use of phenoxy herbicides where exposures of ca. 0.35 mg/kg/day is estimated. Indirect exposure is estimated as being several orders of magnitude lower than the above values at a regional level while consumer exposure to the substance as an impurity in lawn-treatment sprays may be as high as 0.07 mg PCOC /kg/event.

PCOC is corrosive and toxic by inhalation but is only moderately toxic in acute mammalian tests by other routes. The substance is not a skin sensitizer. In an OECD screening test 422, PCOC did not cause reproductive effects in rats. Tests for repeated dose toxicity suggest an NOAEL of 200 mg/kg and a LOAEL of 800/mg/kg (slight liver toxicity and decrease in haemoglobin concentration in the blood). PCOC was positive in an older mouse micronucleus test, but negative in a recent valid test performed according to the current OECD guideline. It did not give rise to genotoxicity in valid Ames tests. On the basis of current knowledge, the substance can not be considered a mutagen.

Repeat dose toxicity is not likely to present a major health problem. The margin of safety for workers based on a NOAEL of 200 mg/kg/day is 200/0.7 = 285. For the end-points irritation/corrosivity the concentration is below the level of concern.

For consumers exposure may be in the order of 0.07 mg/kg for each event corresponding to a daily dose of 9.6×10^{-4} mg/kg/day. With a NOAEL for repeat dose toxicity of 200 mg/kg/day the margin of safety is at least 20,000 for each single event.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

P-chloro-o-cresol (PCOC) is used in the chemical industry as an intermediate in the synthesis of chlorophenoxy herbicides, e.g. MCPA (4-chloro-2-methylphenoxy acetic acid), MCPB (4-chloro-2-methylphenoxy butyric acid), and mecoprop (2-(4-chloro-2-methyl-phenoxy)-propionic acid, MCPP). PCOC is no longer produced in Denmark.

PCOC is found as an impurity in the herbicides MCPA, MCPB, and mecoprop.
During production of PCOC and in the synthesis of other compounds (down stream uses) PCOC is released to the environment through emitted air and waste water. As a degradation product and as an impurity PCOC will also be found at the application sites of the herbicides mentioned above.

PCOC was detected upon branches sprayed with MCPA, 2 weeks post application, at concentrations of 8900 ppb; and upon potatoes, carrots, green lettuce and onions grown on fields adjacent to a treated railway bed in Northern Finland at concentrations of 0.2, 2.9, 52.9 and 593.0 ppb, respectively (Paasivirta *et al.*, 1983).

Concentrations in the environment are estimated in chapter 3.

The most important routes of direct exposure is by inhalation in occupational settings in the production of the substance itself or during use in the synthesis of other compounds (down stream uses). Oral or dermal exposure during production is assumed to be of relevance only in the case of accidents.

Exposure to PCOC as an impurity in herbicides such as MCPA can also occur during crop spraying.

In the Danish Product Register PCOC is only registered as a substance, but was formerly found in one product at a concentration of around 1% in a survey carried out in 1985. With reference to information from industry it is concluded, that no exposure takes place through use of ordinary (non-herbicidal) consumer products.

One potential source of indirect exposure is the consumption of food treated with the herbicides, of which PCOC is a degradation product or an impurity, and drinking of water contaminated by the substance.

4.1.1.2 Occupational exposure

Two companies in the U.K. are high volume producers of PCOC, which is also used as an intermediate for further synthesis at the same sites of the herbicides MCPA, mecoprop, and MCPB. In addition one Dutch high volume producer has been identified, producing PCOC as a non-isolated part of a continuous process which need not be reported under the Regulation. There are no data on occupational exposure available from this producer.

No occupational exposure limits for PCOC have been found but for related substances (cresols and chlorphenols) the values given below apply.

The occupational exposure limit (8-hour threshold limit value (TLV)) for cresols set by the UK and DK authorities (all isomers) is 22 mg/m^3 (HSE 1994, AT, 1994). For chlorphenols (all isomers) the TLV in e.g. Denmark is 0.5 mg/m^3 (AT, 1994).

Production: At one of the production sites, plant operators were monitored at the workplace and tank farm operators were monitored whilst offloading PCOC to the road tanker on four and three occasions, respectively (Road tanker is used to move the substance within the area). According to the manufacturer less than 20 people are involved in these operations (pers. communication, 1997). For the plant operators the monitoring period lasted from 183 to 238 minutes. For the tank farm operators the monitoring period lasted from 15 to 101 minutes. Concentrations for plant operation and offloading to road tankers ranged from below detection limit to about 5 mg/m^3 (equivalent 8 hour TWA's max. ca. 5 mg/m^3) (A.H. Marks, 1997b).

During cleaning operations, which were infrequent (twice per year) and where protective clothing and breathing apparatus was worn, a concentration of about 53.8 mg/m^3 was recorded (8 hr. TWA 1.2 mg/m^3). The monitoring was done at one occasion (A.H. Marks, 1997b). According to the manufacturer, less than 20 people are involved in this operation (pers. comm.). One of the main manufacturers has reported that the exposure actually only applies to one worker. (pers. comm., A.H. Marks, march 6 1998)

Beside the actual operator monitoring point location monitoring in working areas was performed showing TWA values of less than 5 mg/m^3 for all instances (e.g. control room, by reactor, by holding vessels, process scrubber, and whilst offloading PCOC to road tanker) except cleaning of the equipment where a concentration of 1,274.8 mg/m^3 was recorded (equivalent to 8 hr. TWA 18.6 mg/m^3)(A.H. Marks, 1997b).

For production of phenoxy herbicides, which was done at the same plant, monitoring data (operator and point location monitoring) was of a similar order of magnitude, less than 5 mg/m^3 at all occasions. Here cleaning of the equipment was not monitored (A.H. Marks, 1997b). PCOC is used in the molten state, which together with the corrosive nature of the substance, ensures that workers comply fully with PPE requirements (pers. Comm., A.H. Marks, march 6, 1998)

There are no monitoring data on PCOC available from the other U.K. production site. According to the producer the occupational exposure to PCOC is regarded as being minimal, because all vessels and sample points are enclosed and maintained under extraction with air being discharged via caustic scrubbing columns. In addition all employees are provided with appropriate Personal Protective Equipment which is laundered and maintained by the company (Nufarm, 1997b).

According to the producers most of the manufacture and use of PCOC do not require operator intervention. However, there are exceptions e.g. maintenance and tanker loading and unloading. For these operations as well as for emergency situations appropriate PPE are provided including suit (PVC or full body cotton overalls), full face mask, PVC gloves, boots (leather or PVC), safety helmet and glasses (A.H. Marks, 1997b; Nufarm, 1997b).

Assuming inhalation of 10 m^3 of air during an eight hour work shift, for a 70 kg person, 5 mg/m^3 would correspond to a realistic worst case dose for systemic toxicity of about 0.7 mg/kg/day. It can be noted that while this concentration is less that 0.25 of the TLV for cresols and thus meets U.K. regulatory standards, it is 10 times higher than the TLV for chlorphenols, which from a chemical-structural point of view are quite similar to PCOC.

The EASE estimation (app. 5) of inhalation exposure during production and further processing of PCOC assuming use pattern is closed system and the pattern of control is full containment resulted in exposures of 0 to 0.1 ppm corresponding to 0 to 0.6 mg/m^3. This range is much lower than monitored data.

While some degree of dermal exposure may also occur, the EASE model predicts this as being of no consequence when compared with the inhalation route (app. 5). Direct contact with the skin would only happen in the case of accidents, where it could result in systemic toxicity as well as severe burns.

In conclusion the known corrosive nature of PCOC together with its use in the molten form ensures that routine transfer and equipment cleaning amd maintenance operations are performed with strict adherence to PPE requirements, resulting in minimal exposure to workers via both dermal and inhalation routes.

Application[2]: In certain occupational settings such as municipal gardening, worst case exposures may be higher. Using a standard model for plan protection product use (Lundeher, 1992) which also incorporates exposure during mixing and loading, a geometric mean exposure of 0.047 mg/kg/day is calculated for hand-held (knapsack) spraying of 1 ha assuming application of 2 kg/ha MCPA with a 1% content of PCOC and 100 % absorption. The 90th percentile exposure using the same inputs results in a total of 0.35 mg/kg/day.

4.1.1.3 Consumer exposure

PCOC is not found in any ordinary consumer products. It can occur as an impurity or breakdown product in herbicides used for controlling weeds in lawns of private gardens. One such product available in the vegetable section of a Danish super market contains MCPA in concentrations of 5.20 g/l in a one-liter plastic bottle provided with a hand pump for aerosol generation. As this form of dispensation can lead to the highest exposures, a realistic worst case for combined inhalation and dermal exposure of 10% is assumed. If PCOC is present as an impurity at 0.5%, and a further 0.5% is generated by exposure of the aerosol to sunlight, a total exposure to PCOC of 5.2 mg/event, or 0.07 mg/kg/event for a 70 kg person could result.

It is difficult to assess the frequency with which such consumer exposure might occur, directions for use on the particular product only state that it can be used during the entire growth period, but is most effective during periods of rapid growth in May, June, July and August (Source, "Toxan" - Labelling information, Distribution: Bayer Denmark A/S, Gammelager 1, 2605 Brøndby. In addition to MCPA, one liter of this product is also stated to contain 1.50 g Dichloprop-p and 0.32 g Dicamba as active ingredients). Assuming a really worst case of five times application per year the total yearly dose of PCOC would be 5 x 0.07 = 0.35 mg/kg/year (= 9.6x10^{-4} mg/kg/day).

2

During spraying, including mixing of pesticides, using sprayers on tractors the exposure is generally estimated to be around 0.00005% of the amount sprayed in a concentration of 15 g/ha using the best available technology. Using standard spraying equipment the exposure is 0.0002% of the amount sprayed (Lund & Kirknel, 1995).

Using a standard model for plant protection product use (Lundeher, 1992) which also incorporates exposure during mixing and loading, and assuming 2 kg MCPA per ha, with a 1% content of PCOC, a geometric mean exposure of 0.02 mg/kg body weight/day is derived, or for the 90th percentile, 0.28 mg/kg body weight/day for 20 ha of downward vehicle-mounted spraying.