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INTEGRATED CRITERIA DOCUMENT ASBESTOS

EFFECTS

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Table 1. Asbestos fiber penetration into the gastrointestinal mucosa of rats

Route of administration	Daily dose (mg/kg bw)	Type of fiber	Duration	Recovery period	Tissues examined	Analysis	Results(EM) Control	Test	Author(s)
Diet	5000	chrysotile	2 years	1 month	colon	EM	3/240(16)*	6/150(10)*	Donham et al., 1980.
Diet	3000	?	3 months	-	colon	EM	not examined	+	Westlake et al., 1965
Diet (in margarine)	100	chrysotile, crocidolite or amosite	1 year	1 month	intestines	EM	-	1/180(6)*,**	Bolton and Davis, 1976
Diet (in margarine)	100	chrysotile, crocidolite or amosite	2 weeks-1 year	?	intestines	EM	-	-	Bolton and Davis, 1976
Intra-oesophagal (in corn oil)	250	amosite	5 days	1 night	duodenum	PLM, biological effects	-(PLM)	-(PLM)	Meek, 1983; Meek and Grasso, 1983
Intraintestinal (closed cannula; in saline)	appr. 20 (10^{11} fibers of 0.05-25 um length)	amosite	1 hour	-	jejunum	EM	-	+	Storeygard and Brown, 1977

*) Fibers/samples, number in parentheses is number of animals examined

**) Statistical analysis indicated that the amount of fibers penetrating the total gut was, with a probability of 90%, less than 1500 for chrysotile, 550 for crocidolite and 100 for amosite

- = negative
+ = positive, not quantified
? = not reported
EM = electron microscope
PLM = polarizing light microscope

Table 2. Fiber migration from the gastro-intestinal lumen of animals into tissues, organs and fluids outside the gastro-intestinal tract

Route of administration	Calculated daily dose (mg/kg b.w.)	Duration	Cumulative calculated fiber dose (f/g b.w.)	Type of fiber	Recovery period	Tissues examined	Calculated recovery rate **	Analysis	Results(EM) Control	Test	Author(s)
Rat Diet (in margarine)	100 or 100 or 100	25 months	7.6×10^{11} " "	amosite crocidolite chrysotile	until natural death	lungs, liver, spleen, kidney, gut, mesentery, omentum, peritoneal wall, thoracic wall	1.7×10^{-10}	EM	not examined	calculated approximate fiber burden/rat: 3000 amosite, 4500 crocidolite, 52000 chrysotile; % outside g.i. tract: 49/55/67	Bolton et al., 1982
Diet (in corn oil or molasses)	500 of 0.3-50 um fiber length 20% > 5um	6 weeks	2.1×10^{11}	chrysotile	-	blood, omentum, lung, kidney, liver, brain	-	EM	+ (except blood)	lung, kidney and brain fiber concentration sign. elevated	Cunningham et al. 1977
Gavage (in suspension)	50 (2x/week); 65% > 10 um length	lifetime*	1.0×10^{11}	chrysotile	-	kidney cortex	1.3×10^{-11}	EM	0.2 fibers/gram dry tissue	5.3 fibers/gram dry tissue in 17 out of 20 rats	Patel-Mandlik and Millette, 1983a,b
In oleo-margarine	1000- 2000	6 days	6.0×10^{10} - 1.2×10^{11}	amosite	1,2,3,4, 5 weeks	mesentery, kidney, lung	6.3×10^{-12}	EM	+ (no amosite)	+ (amosite in mesentery, lung); some non-amosite	Gross et al., 1974

Table 2. (continued)

Route of administration	Calculated daily dose (mg/kg b.w.)	Duration	Cumulative calculated fiber dose (f/g b.w.)	Type of fiber	Recovery period	Tissues examined	Calculated recovery rate	Analysis	Results(EM) Control	Test	Author(s)
										contamination; total tissue fiber burden 50 fibers/rat	
In margarine	125 + 0.025-125	1 month + 1xsingle	3.8×10^{10} + 2.5×10^{5}-1.3×10^{9}	chrysotile	1-48 hours	hepatic portal blood	-	EM	+ (only fibers < 1um length)	blood fiber count sign. elevated at most time intervals after single dosage; peak at 7 hours (only fibers < 1um length)	Weinzweig and Richards, 198
Intra-oesophagal (needle)	1000	single	1.0×10^{10}	amosite	48 hours	mesentery, kidney, lung	0	EM	+	only in tissues of 1 animal with perforated oesophagus	Gross et al., 1974
Diet	500	3 hours-12 days	7×10^{8} - 6×10^{10}	chrysotile (short range fibers)	-	lymph	0 - 2×10^{-6}	EM	0	13 out of 15 animals positive	Sebastien et 1980
Diet	500	3 hours-12 days	4×10^{7} - 4×10^{8}	chrysotile (intermediate range fibers)	-	lymph	0 - 2×10^{-4}	EM	0	4 out of 8 animals positive	Sebastien et 1980

Table 2. (continued)

Route of administration	Calculated daily dose (mg/kg b.w.)	Duration	Cumulative calculated fiber dose (f/g b.w.)	Type of fiber	Recovery period	Tissues examined	Calculated recovery rate	Analysis	Results(EM) Control	Test	Author(s)
In gelatin capsule	60-120	single	$7-14 \times 10^{8}$	chrysotile	-	lymph	7×10^{-7} - 3×10^{-5}	EM	0	all 5 animals tested were positive	Sebastien et al., 1980
In gelatin capsule	50-150	single	$3-8 \times 10^{8}$	crocidolite	-	lymph	0 - 6×10^{-7}	EM	0	3 out of 5 animals were positive	Sebastien et al., 1980
In margarine	0.025-125	single	2.5×10^{5} - 1.3×10^{9}	chrysotile	1-48 hours	hepatic portal blood	-	EM	+ (only fibers < 1um length)	blood fiber count sign. elevated at 7 hours after single dosage of 125 mg/kg (only fibers < 1um length)	Weinzweig and Richards, 1983
Intragastric injection after laparotomy	appr. 25 (10^{11} fibers of 0.5-2 um length)	single	2.5×10^{8}	chrysotile	4 days	blood, spleen, omentum, lungs, brain, heart	1×10^{-3}	EM	+ (except blood)	blood concentration 0.29×10^{6} fibers/gram - sign. elevated; conc. in omentum considerably but not sign., other conc. slightly but not sign. elevated	Cunningham and Pontefract, 1973; Pontefract, 1974

Table 2. (continued)

Route of administration	Calculated daily dose (mg/kg b.w.)	Duration	Cumulative calculated fiber dose (f/g b.w.)	Type of fiber	Recovery period	Tissues examined	Calculated recovery rate	Analysis	Results(EM) Control	Test	Author(s)
Intragastric injection after laparotomy	appr. 2×10^{10} fibers of 0.5-2 um length)	single	2.5×10^{7}	chrysotile	2 days	blood, spleen, omentum, lungs, brain	0.2	EM	+ (except blood)	blood concentration 4.6×10^{6} fibers/gram - sign. elevated; other conc. slightly but not	Cunningham and Pontefr 1973; Pontefract,
Baboon Gavage	800 mg/kg + 800 mg/kg	9 days	7.2×10^{10}	chrysotile crocidolite	24 hours	stomach, heart, pancreas, blood, kidney, lung, liver, spleen	-	EM	+	sign. elevated chrysotile and crocidolite in heart and blood, chrysotile in stomach and pancreas	Kaczenski and Hallenb 1984
Man In drinking water	"high amphiboles", fiber length 1.5 um, diameter <0.2 um); control population "low amphiboles"	up to 14 years	-	amphibole	-	lungs, jejunum, liver	8×10^{-3}	EM	lung amphibole content***: 0.5×10^{5} fibers/gram jejunum amphibole content***: 0 fibers/gram liver amphibole content***: 0.4×10^{5} fibers/gram	lung amphibole content***: 16.2×10^{5} fibers/gram jejunum amphibole content***: 0.3×10^{5} fibers/gram liver amphibole content***: 5.9×10^{5} fibers/gram	Carter and Taylor, 1980

Table 2. (continued)

Route of administration	Calculated daily dose (mg/kg b.w.)	Duration	Cumulative calculated fiber dose (f/g b.w.)	Type of fiber	Recovery period	Tissues examined	Calculated recovery rate	Analysis	Results(EM) Control	Results(EM) Test	Author(s)
In drinking water	$2x10^8$ fibers/l; control population	1.5-24 yr	$6.7x10^3$	chrysotile	-	urine	0.13	EM	$0.83x10^6$ chrysotile fibers/l	$0.92x10^6$ chrysotile fibers/l	Boatman et al., 1983
	$2x10^6$ fibers/l	3-19 yr	67								
In drinking water	"high amphiboles"; control population filtered water	?	-	amphibole	-	urine	-	EM	$2.3x10^4$ fibers/l	$6.6x10^5$ fibers/l	Cook and Ohlson, 1979
Oral medicine	150 mg/kg of average fiber length 0.8 um	6 months	$2.7x10^{11}$	attapulgite	?	urine	$1x10^{-6}$	?	-	$3x10^5$ fibers/ml	Bignon et al., 1980

*) animals were offspring from asbestos-fed mothers

**) Recovered fibers per g tissue or g b.w. / ingested fibers per g b.w.

***) test samples probably contaminated with amphiboles (Cook, 1983)

Table 3. Animal ingestion studies, carcinogenic effects.

Species	Number of animals (m=male, f=female)	Regimen	Calculated approximate daily dose (mg/kg b.w.)	Fiber type	Effects	Author(s)
Rat (SD)	20	300 mg/day in cottage cheese, lifetime	750	amosite	No increased tumor incidence	Hilding et al., 1981
	20	control	-			
Rat (F344)	100 m, 100 f	10% in diet up to 32 months	500	chrysotile B	No increased tumor incidence, 3/189 adenocarcinoma of colon, 1/189 adenoma of colon, 1/189 mesothelioma in abdomen.	Donham et al., 1980
	100 m, 100 f	10% in diet (positive control)	-	nonnutritive cellulose	No increased tumor incidence, 2/197 adenocarcinomas of colon.	
	100 m, 100 f	control	-	-	3/115 adenocarcinomas of colon.	
Rat (F344)	250 m, 250 f	1% in diet, lifetime	500	shortrange chrysotile	No increased tumor incidence, m 4%, f 5% tumors of alimentary tract.	NTP, 1985
	250 m, 250 f	1% in diet, lifetime	500	intermediate range chrysotile	No increased malignant tumor incidence, increased benign epithelial neoplasms in descending colon of males, m 8%, f 3% tumors of alimentary tract.	
	100 m, 100 f	1% in diet, lifetime + preweaning gavage of similar dose	500	intermediate range chrysotile	No increased tumor incidence, m 7%, f 5% tumors of alimentary tract.	
	88 m,	control		-	M 2%, f 3% tumors of alimentary	

Table 3. (continued)

Species	Number of animals (m=male, f=female)	Regimen	Calculated approximate daily dose (mg/kg b.w.)	Fiber type	Effects	Author(s)
	88 f				tract.	
Rat (F344)	250 m, 250 f	1% in diet, lifetime	500	amosite	Increased C-cell adenomas of thyroid in males (m 20%, f 12%), increased mononuclear leukemia in males (m 42%, f 33%).	McConnell et al., 1983b
	100 m, 100 f	1% in diet, lifetime + preweaning gavage of a similar dose	500	amosite	Increased mononuclear leukemia in males (m 49%, f 34%).	
	118 m, 118 f	control	-	-	Incidence C-cell carcinoma of thyroid m 14%, f 14%, incidence mononuclear leukemia m 32%, f 33%.	
Rat (F344)	250 m, 250 f	1% in diet, lifetime	500	tremolite	No increased tumor incidence	McConnell et al., 1983b
	118 m, 118 f	control	-	-	-	
Rat (Wistar)	40 m	1% in diet, up to 30 months (in 5% corn oil)	500	chrysotile	No increased tumor incidence	Cunningham et al., 1977
	40 m	control	-	-	-	
Rat (Wistar)	22 m	250 mg/week in margarine, 25 months	90	chrysotile A	No increased malignant tumor incidence, increased incidence of benign neoplasms (11/22),	Bolton et al., 1982

Table 3. (continued)

Species	Number of animals (m=male, f=female)	Regimen	Calculated approximate daily dose (mg/kg b.w.)	Fiber type	Effects	Author(s)
					mainly of mesenteric hemangiomas (4/22).	
	24 m	250 mg/week in margarine, 25 months	90	amosite	No increased tumor incidence, 1/24 gastric leiomyosarcoma.	
	22 m	250 mg/week in margarine, 25 months	90	crocidolite	No increased tumor incidence.	
	24 m	margarine-fed control	-	-	No increased tumor incidence.	
	23 m	control	-	-	-	
Rat (SD)	30	20 mg/day, 7 months + 20 mg/day, rest lifespan, in cottage cheese	50	chrysotile amosite	No increased tumor incidence	Hilding et al., 1981
	20	control	-	-		
Rat (SD)	24 m, 16 f	1.5% in diet, cumulative dose 1900 mg in 63 weeks, up to 75 weeks of age	10	crocidolite	No increased tumor incidence in intestinal wall.	Bonser and Clayson, 1967
Rat (Wistar)	16 m, 16 f	100 mg/day; 101 days in 5 months;	250	talc	No increased tumor incidence, 1 leiomyosarcoma of the	Wagner et al., 1977

Table 3. (continued)

Species	Number of animals (m=male, f=female)	Regimen	Calculated approximate daily dose (mg/kg b.w.)	Fiber type	Effects	Author(s)
		lifetime follow-up			stomach.	
	16 m, 16 f	100 mg/day; 101 days in 5 months; lifetime follow-up	250	chrysotile (SFA, super fine with known carcinogenic potency)	No increased tumor incidence, 1(0?) leiomyosarcoma of stomach.	
	8 m, 8 f	control	-	-	-	
Rat (Wistar)	31	10 mg/week in butter for 16 weeks; lifetime follow-up	3.6	chrysotile	No increased tumor incidence.	Gross et al., 1974
	33	5 mg/week in butter for 16 weeks; lifetime follow-up	1.8	crocidolite	No tumors.	
	35	10 mg/week in butter for 16 weeks; lifetime follow-up	3.6	crocidolite	No increased tumor incidence.	
	24	butterfed control	-	-	No tumors.	
Rat (Wistar)	35 + 28	10 mg/week in butter for 18 weeks; lifetime	3.6	crocidolite (2 varieties)	No tumors.	Gross et al., 1974

Table 3. (continued)

Species	Number of animals (m=male, f=female)	Regimen	Calculated approximate daily dose (mg/kg b.w.)	Fiber type	Effects	Author(s)
	24	follow-up control	-	-	No tumors.	
Hamster (Syrian golden)	250 m, 250 f	1% in diet, lifetime	1200	shortrange chrysotile	Increased incidence of primary tumors in males, caused by increase of adrenal cortical adenomas (11%).	McConnell et al., 1983a
	250 m, 250 f	1% in diet, lifetime	1200	intermediate range chrysotile	Increased incidence of primary tumors in males, caused by increase of adrenal cortical adenomas (10%).	
	250 m, 250 f	1% in diet, lifetime	1200	amosite	No increased tumor incidence	
	3x126 m, 3x126 f	control	-	-	Primary tumor incidence m 20%; incidence adrenal cortical adenomas m 3-7%.	
Hamster (Syrian golden)	60	50 mg/l drinking water, up to 23 months	34	amosite	No increased tumor incidence.	Smith et al., 1980 (cited in Toft et al., 1984)
	60	5 mg/l drinking water, up to 23 months	3.4	amosite	No increased tumor incidence, 1 peritoneal mesothelioma.	
	60	0.5 mg/l drinking water, up to 23 months	0.34	amosite	No increased tumor incidence.	
	120	control	-	-	-	

Table 4. Asbestos mass concentration in air related to carcinogenic effects in rats after longterm inhalation.

Species	Number of animals	Asbestos type	Concentration	Duration exposure*	Duration experiment	Effects Lung tumors	Effects Mesothelliomas	Effects Total	Author(s)
Rat	61	chrysotile	86 mg/m3	62 weeks	16-21 months	9/42	1/42	24%	Gross et al., 1967
	40	control	-			3/19		16%	
Rat	69	chrysotile	50 mg/m3	2 years**	?	3/43		7%	Reeves et al., 1974
	69	crocidolite	50 mg/m3	2 years**	?	4/46		9%	
	69	amosite	50 mg/m3	2 years**	?	2/46	1/46	7%	
	10-12	control	-					0%	
Rat (Wistar)	24	Canadian chrysotile	10-11 mg/m3	24 months	24 months	5/21	1/21	29%	Wagner et al., 1974
	20	Zimbabwean chrysotile	10-11 mg/m3	24 months	24 months	10/17		59%	
	20	crocidolite	10-11 mg/m3	24 months	24 months	4/18		22%	
	21	amosite	10-11 mg/m3	24 months	24 months	9/21		43%	
	19	anthophyllite	10-11 mg/m3	24 months	24 months	9/18	1/18	56%	
	48	control	-					0%	
Rat (Wistar)	23	Canadian chrysotile	10-11 mg/m3	12 months	24 months	7/23	3/23	43%	Wagner et al., 1974
	27	Zimbabwean chrysotile	10-11 mg/m3	12 months	24 months	13/27		48%	
	26	crocidolite	10-11 mg/m3	12 months	24 months	9/26	2/26	42%	
	25	amosite	10-11 mg/m3	12 months	24 months	1/25		4%	
	28	anthophyllite	10-11 mg/m3	12 months	24 months	5/28	1/28	21%	
	48	control	-					0%	

Table 4. (continued)

Species	Number of animals	Asbestos type	Concentration	Duration exposure*	Duration experiment	Effects Lung tumors	Effects Mesotheliomas	Effects Total	Author(s)
Rat	48	chrysotile	10 mg/m3	1 year	860 days	8/40		20%	Davis et al., 1978
(Wistar)	48	crocidolite	10 mg/m3	1 year	860 days	0/40		0%	
	48	amosite	10 mg/m3	1 year	860 days	0/43		0%	
	20	control	-					0%	
Rat	48	amosite	10 mg/m3	1 year	29 months	0/40		0%	Davis et al., 1980
(Wistar)	48	control	-					0%	
Rat	48	crocidolite	5 mg/m3	1 year	860 days	0/43	1/43	2%	Davis et al., 1978
(Wistar)	48	chrysotile	2 mg/m3	1 year	860 days	2/42	1/42***	7%	
	48	control	-					0%	
Rat	48	chrysotile	2 mg/m3	1 year	29 months	2/40	1/40	8%	Davis et al., 1980
(Wistar)	48	control	-					0%	
Rat	80	chrysotile	1 mg/m3	18 months	24 months	0/38		0%	Platek et al., 1985
(SD)	80	control	-			0/45		0%	

*) 30-35 hours/week unless otherwise stated

**) 16 hours/week

***) peritoneal mesothelioma; all others pleural mesotheliomas

Table 5. Asbestos fiber concentration in air and fiber size related to carcinogenic effects in rats after longterm inhalation.

Number of animals	Asbestos type	Concentration* (fibers >5um/l)	(mg/m3)	Fiber size characteristics %>5um length	%>20um length	Effects Lung tumors	Mesotheliomas	Total	Author(s)
48	chrysotile	2.0×10^6	10	35%	5%	8/40		20%	Davis et al., 1978
48	crocidolite	8.6×10^5	10	15%	0.5%	0/40		0%	
48	amosite	5.5×10^5	10	18%	0.3%	0/43		0%	
48	crocidolite	4.3×10^5	5	15%	0.5%	0/43	1/43	2%	
48	chrysotile	3.9×10^5	2	35%	5%	2/42	1/42	7%	
69	crocidolite	1.1×10^6 **	50	-	-	4/46		9%	Reeves et al., 1974
69	amosite	8.6×10^5 **	50	-	-	2/46	1/46	7%	
69	chrysotile	5.4×10^4 **	50	-	-	3/43		7%	
48	amosite	-	10	30%	11%	-	-	>30%	Davis (IPCS, 1986)
48	amosite	-	10	1%	-	-	-	0%	
24	UICC chrysotile	3.2×10^6	11	-	-	-	-	UICC gave more lung tumors than Grade 7 (SFA?)	Wagner (IPCS, 1986)
24	Grade 7 chrysotile	1.0×10^6	11	-	-	-	-		
24	SFA chrysotile	4.3×10^5	11	"superfine"		-	-		
80	chrysotile	8.0×10^2 ***	1	<1%	-	0/38	0/38	0%	Platek et al., 1985

- = not reported

*) 30-35 hours/week, 1 year unless otherwise stated

**) 16 hours/week, 2 years

***) counted by light microscope; electron microscopic counting: 3×10^3 f/l

Table 6. Carcinogenic effects of asbestos inhalation in rats in relation to the duration of exposure (from: Wagner et al., 1974).

Number of animals	Asbestos type	Concentration	Duration of exposure (7 hrs/day; 5 days/week)	Duration of experiment	Effects		
					Lung tumors	Mesotheliomas	Total
49	Canadian chrysotile	10 mg/m3	1 day	24 months	1/42		2%
49	Zimbabwean chrysotile	15			1/45		2%
49	crocidolite	13			1/43	1/43	5%
49	amosite	14			0/45	1/45	2%
49	anthophyllite	13			0/44		0%
48	control	-			0/44		0%
52	Canadian chrysotile	12 mg/m3	3 months	24 months	3/34		9%
52	Zimbabwean chrysotile	12			3/39		8%
52	crocidolite	13			2/36	1/36	8%
52	amosite	12			0/37		0%
52	anthophyllite	14			0/37		0%
58	control	-			0/40		0%
24	Canadian chrysotile	10 mg/m3	6 months	24 months	1/17		6%
25	Zimbabwean chrysotile	11			3/19		16%
24	crocidolite	11			0/18		0%
24	amosite	11			1/18		6%
24	anthophyllite	11			2/18		11%
48*	control	-			0/42		0%

Table 6. (continued)

Number of animals	Asbestos type	Concentration	Duration of exposure (7 hrs/day; 5 days/week)	Duration of expriment	Effects		
					Lung tumors	Mesotheliomas	Total
23	Canadian chrysotile	11 mg/m3	12 months	24 months	7/23	3/23	43%
27	Zimbabwean chrysotile	11			13/27		48%
26	crocidolite	11			9/26	2/26	42%
25	amosite	11			1/25		4%
28	anthophyllite	11			5/28	1/28	21%
48*	control	-			0/42		0%
24	Canadian chrysotile	10 mg/m3	24 months	24 months	5/21	1/21	29%
20	Zimbabwean chrysotile	10			10/17		59%
20	crocidolite	10			4/18		22%
21	amosite	11			9/21		43%
19	anthophyllite	11			9/18	1/18	56%
48*	control	-			0/42		0%

Table 7. Differences in exposure regimen (intermittent peak doses versus regular even doses) related to carcinogenic effects in rats after longterm inhalation of asbestos (from: Davis et al., 1978).

Number of animals	Asbestos type	Concentration (mg/m3)*	Hours/week exposure (1 year)	Duration experiment	Effects		
					Lung tumors	Mesotheliomas	Total
48	chrysotile	10 mg/m3	7(1 day)	29 months	2/43		5%
48	chrysotile	2 mg/m3	35(5 days)	29 months	2/40	1/40	8%
48	amosite	50 mg/m3	7(1 day)	29 months	2/44		5%
48	amosite	10 mg/m3	35(5 days)	29 momths	0/40		0%

*) the cumulative fiber dose was approximately the same for all 4 groups

Table 8. Fibrogenicity of asbestos in animals after inhalation for various periods of time.

Species	Asbestos type	Concentration and fiber size				Duration of exposure	Effects (at time of measurement from first exposure)	Author(s)
		mg/m3	f>5um/l	%>5um	%>20um			
		(6-8 hrs/day, 5 days/week unless otherwise stated)						
Rat	crocidolite	50(16hrs/w)	$1.1x10^6$	-	-	2 years	Highest degree of asbestosis for crocidolite	Reeves et al., 1974
	amosite	50(16hrs/w)	$8.6x10^5$	-	-	2 years		
	chrysotile	50(16hrs/w)	$5.4x10^4$	-	-	2 years		
Rat	SFA chrysotile	11	-	"very fine"		1 year	Sligth to moderate fibosis after 1 year with progression after termination of exposure	Wagner et al., 1977
	Italian talc	11	-	-	-	1 year	Very similar fibrosis with progression	
Rat	amosite, anthophyllite, crocidolite, chrysotile (Canadian), chrysotile (Zimbabwean)	10-15	-	-	-	1 day, 8 weeks, 3, 6, 12 and 24 months	Gradually increasing degree of fibrosis with time; amosite slightly less than other varieties; progression with time after termination of exposure (see fig. 1)	Wagner et al., 1974
Rat							At 12 , 18 and 29 months:	Davis et al., 1978
	chrysotile	10	$2.0x10^6$	35%	5%	1 year	19.3, 17.1 and 15.0% peribronchiolar fibrosis**	
	crocidolite	10	$8.6x10^5$	15%	0.5%	1 year	2.7, 4.3 and 3.9%	
	amosite	10	$5.5x10^5$	18%	0.3%	1 year	4.1, 5.1 and 4.2%	
	crocidolite	5	$4.3x10^5$	15%	0.5%	1 year	2.8, 2.3 and 2.5%	
	chrysotile	2	$3.9x10^5$	35%	5%	1 year	10.7, 9.9 and 7.5%	
Rat							At 12 , 18 and 29 months:	Davis et al., 1978
	chrysotile	10	$2.0x10^6$	35%	5%	1 year	0.5, 0.9 and 9.2% interstitial fibrosis**	
	crocidolite	10	$8.6x10^5$	15%	0.5%	1 year	0 , 0.1 and 1.4%	

Table 8. (continued)

Species	Asbestos type	Concentration and fiber size				Duration of exposure	Effects (at time of measurement from first exposure)	Author(s)
		mg/m3	f>5um/l	%>5um	%>20um			
		(6-8 hrs/day, 5 days/week unless otherwise stated)						
	amosite	10	$5.5x10^5$	18%	0.3%	1 year	0.9, 0.1 and 2.6%	
	crocidolite	5	$4.3x10^5$	15%	0.5%	1 year	0.4, 0 and 0.8%	
	chrysotile	2	$3.9x10^5$	35%	5%	1 year	0.4, 0.8 and 3.9%	
Rat							At 12 , 18 and 29 months:	Davis et al., 1980
	amosite	50(1d/w)	-	18%	0.3%	1 year	6.2, 5.4 and 2.9% peribronchiolar fibrosis**	
	amosite	10	$5.5x10^5$	18%	0.3%	1 year	4.1, 5.1 and 4.2%	
	chrysotile	10(1d/w)	-	35%	5%	1 year	6.8, 6.1 and 3.9%	
	chrysotile	2	$3.9x10^5$	35%	5%	1 year	10.7, 9.9 and 7.5%	
Rat							At 12, 18 and 29 months:	Davis et al., 1980
	amosite	50(1d/w)	-	18%	0.3%	1 year	0 , 1.2 and 5.8% interstitial fibrosis**	
	amosite	10	$5.5x10^5$	18%	0.3%	1 year	0.9, 0.1 and 2.6%	
	chrysotile	10(1d/w)	-	35%	5%	1 year	1.3, 1.1 and 6.8%	
	chrysotile	2	$3.9x10^5$	35%	5%	1 year	0.4, 0.8 and 3.9%	
Rat	amosite	10	-	30%	-	1 year	Extensive fibrosis	Davis, 1986
	amosite	10	-	1%	-	1 year	No fibrosis	
Rat	chrysotile	11	-	25%,10%>10um		3 months	Continuing process of interstitial fibrosis	Pinkerton et al., 1984
	chrysotile	11	-	25%,10%>10um		12 months	with increasing lung volume due to thickening of alveolar walls and air trapping	
Rat	chrysotile	1	$0.8\text{-}3x10^3$	<1%	-	18 months	No fibrosis	Platek et al., 1985
Rat	amosite	300	$3.1x10^6$	-	-	90 days	Marked collagenized fibrosis	Lee et al., 1981

Table 8. (continued)

Species	Asbestos type	Concentration and fiber size				Duration of exposure	Effects (at time of measurement from first exposure)	Author(s)
		mg/m3	f>5um/l	%>5um	%>20um			
		(6-8 hrs/day, 5 days/week unless otherwise stated)						
	Fybex*	80	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	
	PKT*	70	$2 x10^6$	-	-	90 days	Very slight collagenized fibrosis	
	fiberglass	400	$7 x10^5$	-	-	90 days	No fibrosis	
Rat	Fybex*	370	$4.2x10^7$	-	-	90 days	Moderate collagenized fibrosis	Lee et al., 1981
	Fybex*	80	$1.4x10^7$	-	-	90 days	Slight collagenized fibrosis	
	Fybex*	40	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	
Rat	chrysotile	11	-	-	-	91 days	First fibrosis at 8 months, no calcification	Ogisho et al., 1984
	crocidolite	11	-	-	-	91 days	Microcalcifications, fibrosis at 8 months	
Rat	chrysotile	-(3hrs/d)	$5x10^6$	26%	2%	30 days	Slight focal collagen formation from day 14 onwards, with progression in interstitium	Holt et al., 1964
	chrysotile	-(1.5hr/d)	$5x10^6$	26%	2%	45 days	Similar lesions, but smaller and less obvious	
Rat	chrysotile	15	-	-	3%	1 hour	Interstitial calcifications after 1 month with thickened alveolar duct bifurcations	Brody and Hill, 1982
Mouse	crocidolite	50(16hrs/w)	$1.1x10^6$	-	-	2 years	Mild to moderate fibrosis	Reeves et al., 1974
	amosite	50(16hrs/w)	$8.6x10^5$	-	-	2 years	Mild to moderate fibrosis	
	chrysotile	50(16hrs/w)	$5.4x10^4$	-	-	2 years	Very sligth fibrosis	
Mouse	chrysotile	11(2hrs/d)	-	-	-	75 days	Diffusely scattered focal fibrotic lesions	Bozelka et al., 1983b
Mouse	chrysotile	11	-	-	-	3 days	By 26 weeks minimal fibrosis in centrialveolar region of lungs	Boorman et al., 1984

Table 8. (continued)

Species	Asbestos type	Concentration and fiber size				Duration of exposure	Effects (at time of measurement from first exposure)	Author(s)
		mg/m3	f>5um/l	%>5um	%>20um			
		(6-8 hrs/day, 5 days/week unless otherwise stated)						
Guinea pig	crocidolite	50(16hrs/w)	$1.1x10^6$	-	-	2 years	Gradually developing fibrosis in all groups	Reeves et al., 1974
	amosite	50(16hrs/w)	$8.6x10^5$	-	-	2 years		
	chrysotile	50(16hrs/w)	$5.4x10^4$	-	-	2 years		
Guinea pig	amosite	300	$3.1x10^6$	-	-	90 days	Marked collagenized fibrosis	Lee et al., 1981
	Fybex*	80	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	
	PKT*	70	$2 x10^6$	-	-	90 days	No fibrosis	
	fiberglass	400	$7 x10^5$	-	-	90 days	No fibrosis	
Guinea pig	Fybex*	370	$4.2x10^7$	-	-	90 days	Moderate collagenized fibrosis	Lee et al., 1981
	Fybex*	80	$1.4x10^7$	-	-	90 days	Slight collagenized fibrosis	
	Fybex*	40	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	
Hamster	amosite+ chrysotile	1	$1.3x10^4$	-	-	15 months	Sligth pulmonary fibrosis only after 15 months, sligth increased emphysema after 6 months but not after 15 months	Wehner, 1986
	amosite+ chrysotile	10	$1.2x10^5$	-	-	15 months		
Hamster	amosite	300	$3.1x10^6$	-	-	90 days	Marked collagenized fibrosis	Lee et al., 1981
	Fybex*	80	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	
	PKT*	70	$2 x10^6$	-	-	90 days	Very slight collagenized fibrosis	
	fiberglass	400	$7 x10^5$	-	-	90 days	No fibrosis	
Hamster	Fybex*	370	$4.2x10^7$	-	-	90 days	Moderate collagenized fibrosis	Lee et al., 1981
	Fybex*	80	$1.4x10^7$	-	-	90 days	Slight collagenized fibrosis	
	Fybex*	40	$2.9x10^6$	-	-	90 days	Very slight collagenized fibrosis	

Table 8. (continued)

Species	Asbestos type	Concentration and fiber size				Duration of exposure	Effects (at time of measurement from first exposure)	Author(s)
		mg/m3	f>5um/l	%>5um	%>20um			
		(6-8 hrs/day, 5 days/week unless otherwise stated)						
Rabbit	crocidolite	50(16hrs/w)	$1.1x10^6$	-	-	2 years	Ligth to intermediate fibrosis in survivors	Reeves et al., 1974
	amosite	50(16hrs/w)	$8.6x10^5$	-	-	2 years	Ligth to intermediate fibrosis in survivors	
	chrysotile	50(16hrs/w)	$5.4x10^4$	-	-	2 years	Very sligth fibrosis in survivors	
Baboon	crocidolite	16	$1.1x10^6$	mean 1xd: 2x0.3um		lifetime	Slightly progressing fibrosis	Goldstein et al., 1983
	glass fiber	8	$1.1x10^6$	6x0.5um		lifetime	Similar lesions but less extensive	
Gerbil	crocidolite	50(16hrs/w)	$1.1x10^6$	-	-	2 years	Ligth to moderate fibrosis, focal and generalized alveolar proteinosis especially in amosite/crocidolite groups	Reeves et al., 1974
	amosite	50(16hrs/w)	$8.6x10^5$	-	-	2 years		
	chrysotile	50(16hrs/w)	$5.4x10^4$	-	-	2 years		

*)PTK = pigmentary potassium titanate; Fybex = potassium octatitanate

**) calculated % of lung tissue that was fibrotic

Table 9. Fibrogenic effects of asbestos in animals after intratracheal instillation

Species	Asbestos type	Administered dose(mg)	Regimen	Effects	Author(s)
Rat	UICC chrysotile	5 (20mg/kg b.w.)	single administration	Significant fibrotic reactions from day 7 onwards	Lemaire et al., 1985
	Very short 4T30 chrysotile	5 (20mg/kg b.w.)	single administration	Inflammation (alveolitis), no fibrosis	
Hamster	Chrysotile	5 (40mg/kg b.w.)	single administration	Progressing interstitial fibrosis with air flow obstruction and air trapping in secluded alveoli	Glassroth et al., 1984
Guinea pig	Amosite	30 (40mg/kg b.w.)	single administration	Asbestosis begins at any site in the parenchyma to which the fibers gain access; at 6 months similar response in both groups	Filipenko et al., 1985
		10 (13mg/kg b.w.)	single administration		
Guinea pig	Crocidolite short:<1% >5um length	25 (33mg/kg b.w.)	adminstered in 7-8 instillations	No fibrosis	Wright and Kuschner, 1977
	Crocidolite long:>80% >10um length	4 (5mg/kg b.w.)	" " "	Extensive interstitial fibrosis	
	Synthetic fluor amphibole short: <1% >5um lenght	12 (16mg/kg b.w.)	" " "	No fibrosis	
	Synthetic fluor amphibole long: 43%>5um, 16%>10um length	12 (16mg/kg b.w.)	" " "	Extensive interstitial fibrosis	
	Glass fiber short:7%<10um	25 (33mg/kg b.w.)	" " "	No fibrosis	

Table 9. (continued)

Species	Asbestos type	Administered dose(mg)	Regimen	Effects	Author(s)
	length Glass fiber long: 92%>10um length	12 (16mg/kg b.w.)	" " "	Minimal but definite fibrotic lesions	
	Very thin glass fiber short: 100%<5um length	25 (33mg/kg b.w.)	" " "	No fibrosis	
	Very thin glass fiber long: 50%>10um length	12 (16mg/kg b.w.)	" " "	Minimal but definite fibrotic lesions	
Guinea pig	Amosite	17.5 (23mg/kg b.w.)	single administration	Early effects (1-7 days) only alveolar, not interstitial: formation of small fibrin bundles within alveoli from 2 hours post-dosage onwards; regressing increased permeability of alveolar epithelium	Dodson et al., 1983, 1984
Sheep	Chrysotile	126 (3.2mg/kg b.w.)	1x/month during 6 months, 1x/week during next 6 months	Macrophage infiltrates into interstitium, with alveolitis, narrowed small airways and obstructed airflow	Begin et al., 1983
	Chrysotile	2 (0.05mg/kg b.w.)	" " "	No effects	

Table 10. Fibrous materials producing malignant neoplasms following intraperitoneal or intrapleural injection or implantation (Leineweber, 1980; Wagner et al., 1985; Pott, 1986).

Actinolite	Dawsonite
Aluminium oxide	Erionite
Aluminium silicate glass	Fibrous glass
Amosite	Mineral wool
Anthophyllite	Potassium titanite
Attapulgite	Silicone carbide
Borosilicate glass	Sodium aluminium carbonate
Chrysotile	Tremolite
Crocidolite	Wollastonite

Table 11. Correlation coefficients of logit of tumor probability with common logarithm of number of particles per microgram in different dimensional ranges (Stanton et al., 1981).

Fiber diameter, μm	Fiber length, μm		
	≤4	>4-8	>8
>4		-0.28	-0.30
>1.5-4	-0.45	-0.24	0.13
>0.25-1.5	0.01	0.45	0.68
≤0.25	0.20	0.63	0.80

Table 12. Some characteristics of epidemiological studies with asbestos in drinking water (Marsh, 1983; Erdreich, 1983; Toft et al., 1984).

Study area	Maximum duration of exposure (years)	Population size of studied area	Estimated exposure level ($\times 10^6$ f/l)	Type of fiber	Years of assessment of incidence(i)/ mortality(m)	Reference
Quebec	>50	30,000	1.1-1300	chrysotile	1964-1973(m)	Wigle, 1977
Canada	>50	110,000	0-1800	chrysotile	1966-1976(m)	Toft, 1981; Toft and Meek, 1983
California	>40	1,000,000*	0.016-36	chrysotile	1969-1971(i)	Kanarek et al., 1980
					1969-1975(i)	Conforti et al., 1981
Washington	>40	78,000*	0-556	chrysotile	1974-1977(i),	Polissar et al., 1982
		23,000*			1955-1975(m)	
Utah	20-30	24,000	n.r.	chrysotile	1967-1976(i)	Sadler et al., 1984
Florida	>25	46,000*	<1-10	chrysotile	1963-1976(m)	Millette et al., 1983
Connecticut	20	576,800	<0.1-0.7	chrysotile	1935-1973(i)	Harrington et al., 1978
					1955-1975(i)	Meigs et al. (cited by Meigs, 1983)
Minnesota	0-15	100,000	1-30	amphibole	1950-1969(m)	Mason et al., 1974 (cited by Marsh, 1983)
	15-20				1969-1971(i)	Levy et al., 1976
					1969-1974(i,m)	Sigurdson et al., 1981
	20-25		2-64		1969-1980(i)	Sigurdson, 1983

n.r. = not reported, probably low

*) high exposure subpopulation size

Table 13. Summary of studies of GI cancer risk in relation to ingested asbestos by site of neoplasm (adapted from Marsh, 1983; Erdreich, 1983).

Studied area	Site of neoplasm									All GI sites combined	Reference
	Esophagus	Stomach	Small intestine	Colon	Rectum	Biliary passage/ liver	Gall bladder	Pancreas	Peritoneum		
Quebec	00	M0	-	00	00	-	-	0F	-	00	Wigle, 1977
Canada	00	M0	-	00	00	-	-	00	-	M0	Toft, 1981; Toft and Meek, 1983
California	0F	MF	00	00	00	00	0F	0F	MF	MF	Kanarek et al., 1980
	MF	MF	00	M0	00	00	00	MF	0F	MF	Conforti et al., 1981
Washington	00	00	MF	00	00	00	00	00	00	-	Polissar et al., 1982
Utah	-	00	00	00	00	-	0F	00	00	-	Sadler et al., 1984
Florida	-	-	-	-	-	-	-	00	-	00	Millette et al., 1983
Connecticut	-	00	-	00	00	-	-	-	-	-	Harrington et al., 1978
	-	00	-	00	00	-	-	M0	-	-	Meigs et al. (cited by Meigs, 1983)
Minnesota	M0	MF	-	00	MF	00	-	0F	MF	MF	Mason et al., 1974 (cited by Marsh, 1983)
	00	M0	00	00	00	00	00	MF	00	00	Levy et al., 1976
	00	00	00	00	00	00	00	0F	00	00	Sigurdson et al., 1981

Positive association with ingested asbestos: M=present in males, F=present in females, 0=absent, -=not studied

Table 14. Summary of studies of non-GI cancer risk in relation to ingested asbestos by site of neoplasm (adapted from Marsh, 1983; Erdreich, 1983).

Studied area	Site of neoplasm									Reference
	Buccal cavity/ pharynx	Bronchus/ trachea/ lungs	Pleura	Prostate	Kidneys	Bladder	Brain/ CNS	Thyroid	Leukemia/ aleukemia	
Quebec	00	M0	-	0	00	00	00	-	00	Wigle, 1977
Canada	00	M0	-	0	00	00	00	-	00	Toft, 1981; Toft and Meek, 1983
California	-	M0	0F	0	0F	00	00	00	00	Kanarek et al., 1980
	-	00	0F	M	00	00	00	00	00	Conforti et al., 1981
Washington	00	00	-	M	00	00	M0	MF	M0	Polissar et al., 1982
Utah	-	-	-	-	M0	-	-	00	M0	Sadler et al., 1984
Florida	-	00	-	-	-	-	-	-	-	Millette et al., 1983
Connecticut	-	-	-	-	-	-	-	-	-	Harrington et al., 1978
	-	00	-	-	00	00	-	-	-	Meigs et al. (cited by Meigs, 1983)
Minnesota	-	M0	-	-	-	-	00	-	00	Mason et al., 1974 (cited by Marsh, 1983)
	-	-	-	-	-	-	-	-	-	Levy et al., 1976
	-	00	-	-	-	-	-	-	-	Sigurdson et al., 1981

Positive association with ingested asbestos: M=present in males, F=present in females, 0=absent, -=not studied

Table 15. Standardized mortality ratios (SMR) for cancers of the lung, GI tract and other sites, and number of deaths from mesothelioma and asbestosis in asbestos workers in various occupations. (Numbers of deaths in parentheses)

Type of exposure	Males Females	Cohort size	Years of follow-up	Years from onset exposure	SMR		Number of deaths			Other cancer significantly elevated	Reference
					Lung cancer	GI cancer	Mesothelioma pleural	Mesothelioma peritoneal	Asbestosis		
INSULATION WORKERS											
Mixed	M	632	1943-76	20+	7.10* (93)	2.91* (43)	11	27	41		Selikoff et al., 1979
	M	152	1945-65	15+	7.02* (10)	2.78* (5)	1	2	2		Kleinfeld et al., 1967
	M	170	1940-75	-	5.40* (27)	13.00* (13)	8	5	19		Elmes and Simpson, 1977
	M	17800	1967-76	20+	4.16*(390)	1.67* (89)	63	112	168	Kidneys, larynx, pharynx, buccal cavity	Selikoff et al., 1979
GAS MASK MANUFACTURERS											
Crocidolite	MF	199	1939-75	-	8.75* (7)		3	6	4		McDonald and McDonald, 1978
	F	523	1951-77	10+	2.73* (10)	0.65 (7)	9	3	1	Ovary	Wignall and Fox, 1982
	F	757	1951-80	10+	1.97* (13)	1.25 (5)	3	2		Ovary	Acheson et al., 1982
	F	951	1941-78	-	1.90* (12)	0.49 (10)	13	4			Jones et al., 1980
Chrysotile	F	570	1951-80	10+	1.33 (6)	0.82 (4)	1	0			Acheson et al., 1982
MANUFACTURING											
Mixed	F	922	1936-75	10+	8.43* (27)	1.96* (20)	13	8	6.7		Newhouse and Berry, 1979
	MF	689	1959-71	20+	3.21* (27)	2.66* (13)	8	7	24		Nicholson , 1976
	M	1075	1941-73	Ret.	2.70* (63)	1.38* (55)	5	0	50		Henderson and Enterline, 1979
	M	4600	1936-75	10+	2.38*(103)	1.18 (40)	19	27	16.3		Newhouse and Berry, 1979
Amosite	M	820	1961-76	5+	3.08* (83)	1.23 (28)	7	7	30		Seidman et al., 1979
	M	4820	1947-78	-	1.96* (57)	1.11 (19)	4	1	8.9		Acheson et al., 1984
Chrysotile	M	254	1945-74	-	0.93 (4)	1.05 (4)	0	0			Weiss, 1977

Table 15. (continued)

Type of exposure	Males Females	Cohort size	Years of follow-up	Years from onset exposure	SMR		Number of deaths				Other cancer significantly elevated	Reference
					Lung cancer	GI cancer	Mesothelioma pleural	Mesothelioma peritoneal		Asbestosis		
TEXTILES												
Chrysotile	F	554	1940-75	-	8.24* (14)	1.33 (8)	1	1	2**	13.1		Robinson et al., 1979
	M	1261	1940-75	15+	3.36* (33)	1.24 (10)	0	1		17		Dement et al., 1983a,b
	MF	1493	1940-64	-	2.23* (33)	1.80* (16)	1	8		31		Mancuso and El-Attar, 1967
	M	822	1933-74	10+	2.14* (49)	1.02 (16)	9	0		20.6		Peto, 1977
	M	2543	1938-77	20+	2.00* (59)	1.52* (26)	0	1		20		McDonald et al., 1983a,b
	M	2722	1940-75	-	1.36* (49)	1.21 (50)	4	5	4**	59.5		Robinson et al., 1979
	M	4137	1938-77	20+	1.05 (53)	1.13 (54)	10	4		59		McDonald et al., 1983b
ASBESTOS CEMENT INDUSTRY												
Mixed	M	241	1963-80	15+	6.06* (20)	1.60 (4)	6	5		5.5		Finkelstein, 1983
	M	598	1957-80	10+	1.83* (12)	1.76* (19)	4	0		10.1		Albin et al., 1984
	M	5645	1940-74	20+	1.04 (51)	0.50 (25)	0	0				Weill, 1984
Chrysotile	M	1592	1936-77	15+	0.85 (22)	0.99 (14)	2	0		0		Thomas et al., 1982
MINING												
Chrysotile	M	544	1961-77	20+	2.25* (25)	1.05 (10)	1			26		Nicholson et al., 1979
	M	9767	1926-75	20+	1.25*(230)	1.03 (209)	10	0		46		McDonald et al., 1980
	M	952	1946-75	20+	1.03 (9)	1.03 (15)	1	0		21.1	Larynx	Rubino et al., 1979
	F	440	1926-75	20+	0.83 (1)		1	0		0		McDonald et al., 1980
Crocidolite	M	6200	1938-78	15+	1.57* (60)		17	0		14		Hobbs et al., 1980
Anthophyllite	MF	1092	1936-69	-	1.67* (21)	0.47 (7)	0	0		13		Meurman et al., 1974
Talc	M	260	1944-69	15+	2.89* (13)	1.01 (7)	0	1		29		Kleinfeld et al., 1974
(tremolite)	M	398	1947-75	-	2.70* (9)	1.00 (3)	0	0	1**	3.7		Brown et al., 1979
SHIPYARD ACTIVITIES												
Mixed	M	4264	1960-75	-	2.24*(123)	1.36 (66)				50.6	Kidney, urinary organs, larynx	Puntoni et al., 1979
	M	4779	1950-70	20+	1.73 (13)	-	0	0				Kolonel et al., 1980

Table 15. (continued)

Type of exposure	Males Females	Cohort size	Years of follow-up	Years from onset exposure	SMR		Number of deaths			Other cancer significantly elevated	Reference
					Lung cancer	GI cancer	Mesothelioma pleural	Mesothelioma peritoneal	Asbestosis		
	M	6292	1947-78	-	0.84 (84)	0.83 (63)		31**	9		Rossiter and Coles, 1980
FRICTION PRODUCTS MANUFACTURING											
Chrysotile	M	3177	1938-77	20+	1.49* (73)	1.14 (59)	0	0	0		McDonald et al., 1984
Mixed	M	7474	1942-80	10+	1.03 (143)	0.96(103)	8	0			Berry and Newhouse, 1983
	F	3708	1942-80	10+	0.53 (6)	1.06 (29)	2	0			Berry and Newhouse, 1983

*) significant at the 5% level

**) unspecified mesotheliomas.

Table 16. Deaths among 17,800 asbestos insulation workers in the United States and Canada, January 1, 1967 - December 31, 1976, number of men 17,800, man-years of observation 166,853 (adapted from Selikoff et al., 1979).

Underlying cause of death	Number of deaths			Ratio observed/expected	
	Expected*	Observed			
		BE	DC	BE	DC
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Peritoneal mesothelioma	-	112	24	-	-
Pleural mesothelioma	-	63	25	-	-
Mesothelioma, n.o.s.	-	0	55	-	-
Cancer of lung	105.6	486	429	4.60	4.06
Cancer of kidney	8.1	19	18	2.36	2.23
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx/ buccal cavity	10.1	21	16	2.08	1.59
Cancer of skin	6.6	12	8	1.82	1.22
Cancer of colon/ rectum	38.1	59	58	1.55	1.52
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of prostate	20.4	30	28	1.47	1.37
Cancer of brain	10.4	14	17	1.35	1.63
Cancer of pancreas	17.5	23	49	1.32	2.81
Leukemia	13.1	15	15	1.15	1.15
Cancer of testes	1.9	2	1	1.05	0.52

Table 16. (continued)

Underlying cause of death	Number of deaths			Ratio observed/expected	
	Expected*	Observed			
		BE	DC	BE	DC
Cancer of bladder	9.1	9	7	0.99	0.77
Lymphoma	20.1	19	16	0.95	0.80
Cancer of liver/biliary passages	7.2	5	19	0.70	2.65
All other cancer	25.5	55	92	2.16	3.61
Noninfectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	-	168	78	-	-
All other causes	1280.2	1064	1161	0.83	0.91

*) Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976

BE = Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical)

DC = Number of deaths as recorded from death certificate information only

\- = Rates and thus ratios are not available, but these have been rare causes of death in the general population

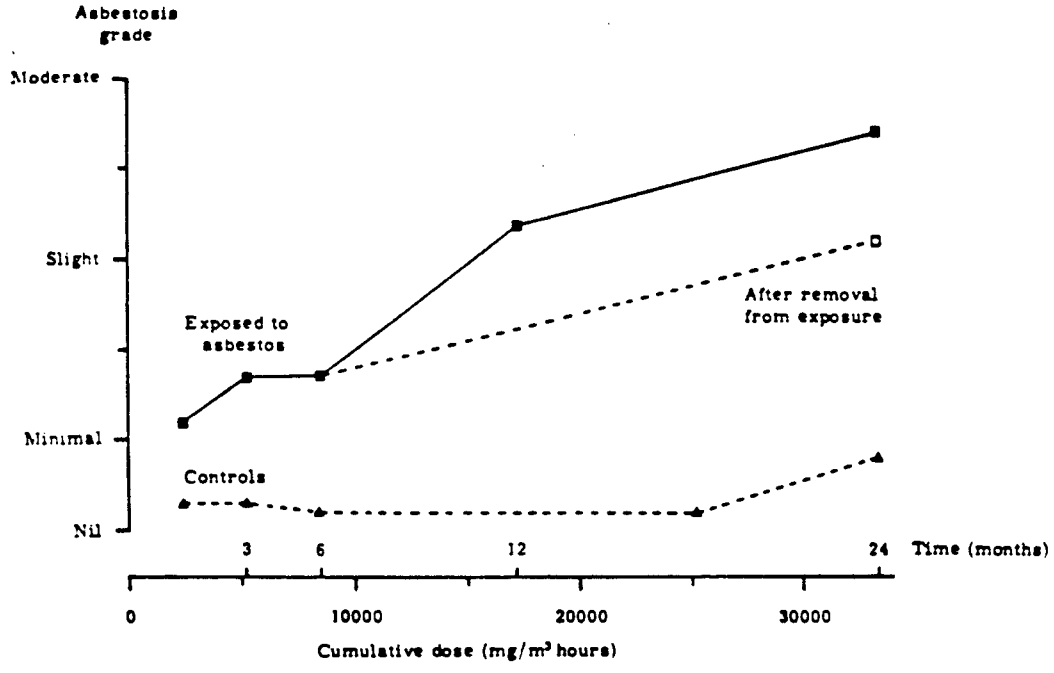

Fig. 1. Asbestosis in sacrificed rats in relation to dose and time (Wagner et al., 1974).

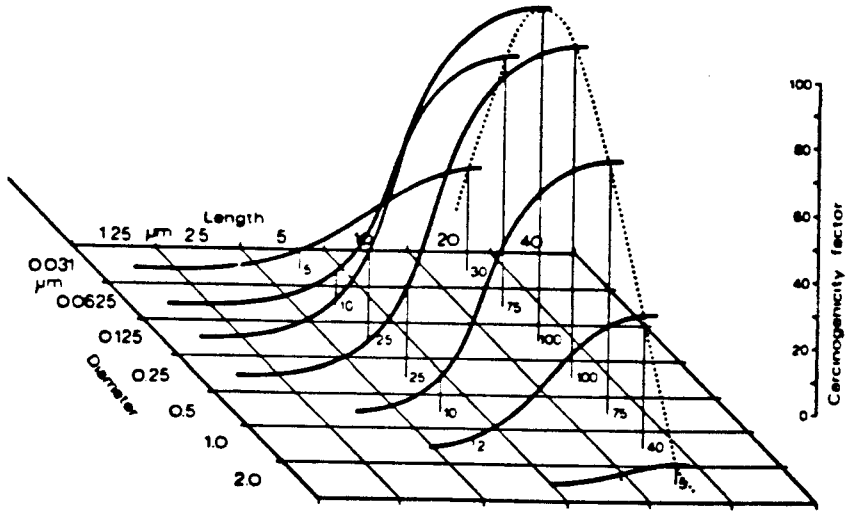

Fig. 2. Hypothesis on the carcinogenic potency of a fiber as a function of its size with some data on "carcinogenicity factors" (Pott, 1978).

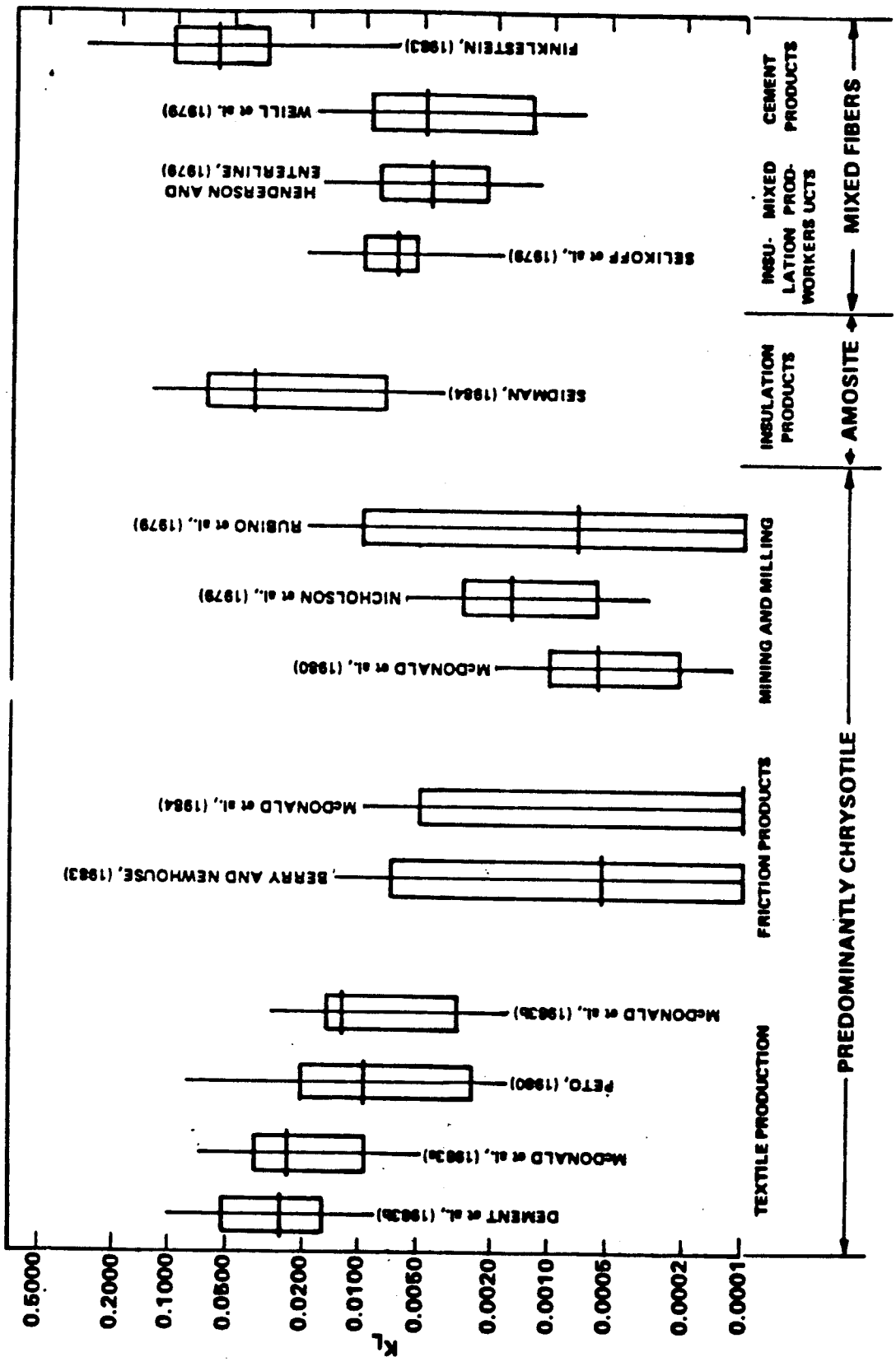

Figure 3 . Values of K_L, the fractional increase in lung cancer per f-y/ml of exposure in 14 asbestos exposed cohorts. The open bar reflects the estimated 95% confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, g rally ± a factor of two.

INTRODUCTION

Asbestos is a general term applied to certain fibrous forms ("asbestiform" varieties) of silicate minerals, with long thin separable fibers or fibrils possessing high tensile strength and flexibility. A fiber is defined as a needle-shaped particle with a length:diameter ratio (= aspect ratio) of > 3:1. Current use of the term asbestos is restricted to six fibrous silicates: chrysotile, crocidolite, amosite, anthophyllite, tremolite and actinolite.
Chrysotile belongs to the mineral group of serpentines, the other five asbestos varieties belong to the mineral group of amphiboles. Chrysotile has the molecular structure $Mg_3(Si_2O_5)(OH)_4$; the amphiboles have the overall formula $(X,Y)_7(Si_8O_{22})(OH)_2$ in which X and Y are cations, mostly Mg and Fe, but also Na, Ca, etc. Non-fibrous varieties of the mentioned six asbestos minerals have virtually the same chemical composition and basic crystal structural components, but differ in crystal form. Those varieties are usually not called asbestos; they may sometimes be called "non-fibrous asbestos" or "non-fibrous chrysotile, crocidolite etc." but they are usually indicated by their mineral names, e.g. Riebeckite (for the crocidolite mineral), Cummingtonite-Gruenerite (for the amosite mineral).
There are many other "asbestiform" minerals, with crystal-forming properties similar to asbestos, that occur naturally. They usually do not possess the same physical-chemical properties as asbestos, and hardly ever occur in sufficient quantities for exploitation. Examples of commercially applied asbestiform minerals are attapulgite and sepiolite. There are also many asbestiform man-made materials, e.g. glass wool, rock wool, ceramic fibers (Walton, 1982; NRC, 1984).
The focus of this document will be on asbestos; some attention will be paid to non-asbestos fibrous materials, but the reviewed literature on the latter subject is not exhaustive.

CAS registry number, names and synonyms of the six commercial asbestos varieties

Name	CAS nr.	Synonyms	Mineral group
Chrysotile	12001-29-5	white asbestos	serpentine
Crocidolite	12001-28-4	blue asbestos, Riebeckite	amphibole
Amosite	12172-73-5	brown asbestos, Cummingtonite-Gruenerite	amphibole
Antophyllite	17068-78-9		amphibole
Actinolite	13768-00-8		amphibole
Tremolite	14567-73-8		amphibole

1. CHEMOBIOKINETICS AND METABOLISM

1.1. Uptake

1.1.1. Oral

Animals

There has been some dispute in literature whether ingested asbestos fibres are able to pass through the gastrointestinal (GI) wall. If fibres are able to cross the GI wall, they may do so by persorption (a mechanism described by Volkheimer, 1974), or by direct penetration through the GI wall due to their sharp needle-like structure. However, experimental evidence (both qualitative and quantitative) of the penetration of ingested fibres into the bloodstream and tissues outside the GI tract is conflicting. This may partly be due to insensitive techniques, experimental artefacts and contamination (Toft et al., 1984; Cook, 1983). Data are given in tables 1 and 2. Despite these conflicting data, the observation of a time-related increase in the asbestos concentration in hepatic portal blood of rats after a single oral dose is evidence for the crossing of the GI wall that must be heavily weighted. A peak appeared 7 hours after asbestos ingestion; if the single dose was preceeded by one month of asbestos feeding the blood fibre levels were considerably higher, at all examined time intervals, but again a peak appeared at 7 hours after ingestion (Weinzweig and Richards, 1983).

The recovery of a relatively higher proportion of long fibres (> 4 μm length) from the lymph of rats, compared with the proportion of those fibres found in administered dietary chrysotile or crocidolite, suggested the preferential uptake of longer fibres from the GI tract (Sebastien et al., 1980). However, very long fibres (32-128 μm) were found in lymph that did not at all occur in feed, which is an indication of contamination or exposure from other sources that greatly reduces the importance of these findings. Contrary to these results, in studies of Weinzweig and Richards (1983) and Cunningham et al. (1977) the mean length of asbestos fibres present in rat blood was found to be smaller than the mean length of ingested chrysotile fibres. This may indicate a preferential absorption of shorter fibres, but it may also be a consequence of the breakdown of fibres in the body (see also 1.3.1.).

The highest reported fibre concentration in animal tissue was approximately 5 x 10^6 fibres/g rat blood, whereas the corresponding single intragastric dose - by coincidence the lowest asbestos dose giving positive evidence of fibre migration- was approximately 2.5 x 10^7 fibres/g body weigth (Cunningham and Pontefract, 1973). However, this dose was given by injection through the opened abdomen, which is a method very liable to damage of tissues and increase in artefactual GI absorption. From dietary studies, using much higher doses of asbestos (details presented in tables 1 and 2), the amount of fibres recovered per gram tissue was 10^{-11} -10^{-10} times lower than the corresponding cumulative ingested dose per gram body weight (calculated with a conversion factor of 10^{10} fibres per mg asbestos; Cunningham and Pontefract, 1973). The similarly calculated recovery rate of ingested fibres from rat lymph ranged from 10^{-7} to 10^{-4} (Sebastien et al., 1980). It can therefore be concluded that the proportion of ingested fibres which cross the GI wall and penetrate into tissues outside the GI tract of rats is very small.

Man

Evidence suggestive of migration of ingested fibres through the GI wall in humans is the observed relatively high fibre content of tissues and urine in residents of areas with a high asbestos concentration in drinking water. However, the results of very similar human studies are contradictory. In the study providing the most suggestive evidence of fibre penetration (Carter and Taylor, 1980), test samples -but not control samples- may have been contaminated with fibre-containing tap water (Cook, 1983). Cook and Ohlson (1979) estimated that, in a group of 8 volunteers, 1:1000 amphibole fibres ingested with drinking water were eliminated in urine, which would indicate a higher uptake than seen in animals. However, urinary recovery of the ingested asbestos-like mineral attapulgite was much lower (see 1.4.1). Data are given in table 2.

1.1.2. Dermal

The only data found concerning the uptake of asbestos or other mineral fibres through the skin were found in a review summarizing relevant Soviet literature concerning asbestos. Local invasion of asbestos fibres into the epidermis of fingers, hands, toes, soles and shins of asbestos workers was reported (IRPTC, 1982). This route of exposure may not be very important, since the skin and underlying tissues have not been reported to be involved in asbestos-related disease in humans, nor in animals, whereas cells and tissues into which fibres

are able to penetrate usually show some degree of abnormality (see 2.2 and 2.5).

1.1.3. Inhalation

Deposition

The general mechanisms by which inhaled particles may be deposited in the respiratory tract (interception, impaction, electrostatical attraction, gravitational settling, Brownian diffusion) have been described in detail in the Criteria Document "Fine Particulate Matter" (Prins et al., 1985). Although interception and electrostatical attraction are not very important for the deposition of spherical particles, they may be for mineral fibres (Lippmann et al., 1980). Deposition by interception depends mainly on fibre length; longer fibres are more easily intercepted than shorter fibres. Furthermore, freshly fractured mineral dust fibres can have an increased static electricity, which enhances deposition by electrostatic attraction in the respiratory tract (Lippmann et al., 1980). Electrostatic charging of amosite fibres caused up to 40% enhancement of dust deposition in the pulmonary region of rats (Vincent et al., 1981).

Deposition by impaction depends mainly on the aerodynamic equivalent fibre diameter (Dae), which is approximately 3-4 x larger than the actual diameter for amosite and glass fibres, and probably for all other amphiboles, and relatively independent of fibre length. For chrysotile a Dae is more difficult to assess, because chrysotile fibres tend to be curved and therefore behave differently (Gross, 1981). Particles with large Dae impact preferentially in the nasopharynx and the tracheobronchial region, although the deposition by diffusion of particles with a Dae much smaller than 0.01 μm may also be high in these regions. Particles with Dae between 0.1 and 2 μm are for a large part deposited in the alveolar region of the lungs (Lippmann et al., 1980). This relationship between mean Dae and deposition was clearly demonstrated for various asbestos types by rat single inhalation experiments (Morgan et al., 1975).

The upper limit of respirability for long fibrous particles is approximately 10 μm Dae, which corresponds with 3.5 μm fibre diameter for straight fibre types, and 200 μm fibre length. These values were established from human data (lung fibre contents) as well as from rat inhalation experiments (Lee, 1985).

The total amounts of deposited chrysotile A, chrysotile B, amosite, crocidolite, anthophyllite and a fluoramphibole in rats, expressed as

percentage of inhaled material, were 31, 43, 42, 41, 64 and 68%, respectively, of which 29-38% in the alveolar region of the lungs, 3-9% in the nasal passage, 51-67% in the GI tract (originating from clearance -see Clearance/retention), and 1-2% in the oesophagus (Morgan et al., 1975). Similar findings were reported for irradiated crocidolite in rats (Evans et al., 1973) and in Beagle dogs (Griffis et al., 1983).

Clearance/retention

The International Commission on Radiological Protection (ICRP) assumes a halftime of 4 minutes for physical clearance from the human nasopharyngeal region, which mainly takes place via the mucociliary escalator and subsequent swallowing/expectoration (Raabe, 1984).

The primary clearance mechanism in the tracheobroncheal region is also mucociliary transport and swallowing/expectoration. This can be accelerated by coughing. The approximate clearance halftime for the larger airways in this region is 0.5 hr, for intermediate airways in this region 2.5 hr and for finer airways in this region 5 hr in humans (Raabe, 1984).

Insoluble particles like asbestos, deposited beyond the ciliated airways, are removed very slowly. Halftimes of clearance of insoluble particles from the deep lung for man have been estimated from data on dogs and monkeys to be 1-2 years (Lippmann et al., 1980; Raabe, 1984). Particles entering this region are rapidly phagocytized by pulmonary macrophages; in rats, free fibres were observed entering the underlying epithelial cells, the interstitium, the basement membranes or even the endothelial cells of capillaries (Brody and Hill, 1981; Pinkerton et al., 1984). In vitro studies (see 2.5) have shown that fibres with length < 3 μm are usually completely engulfed by macrophages; fibres with length > 5 μm may be incompletely phagocytized, with part of the fibres being uncovered. Fibres with diameter > 3 μm are not taken up by macrophages (Beck and Tilkes, 1980).

Migration and grouping of particle-containing macrophages leads to redistribution of evenly dispersed particles into clumps and focal aggregations of particles, mostly in the periphery of the lung and subpleurally (Raabe, 1984). In rodents, particle-containing macrophages may be carried to the tracheobronchial region by a flow of pulmonary liquid, whereas in humans this flow appears to be only minimal (Raabe, 1984).

Gross et al. (1967) reported that intratracheal treatment with NaOH affected mucociliary clearance in rats, resulting in increased retention of inhaled fibres. The effect of smoking on the deposition and retention of asbestos is

not exactly known. Irritants in smoke may alter the properties of lung surfactant, and smoke is known to have bronchoconstrictive properties, which increase particle deposition; on the other hand, inhalation of smoke may change the breathing pattern and increase the exhalation of air and particles; enhanced mucus secretion resulting from smoking may also cause increased clearance (Lippmann et al., 1980).

Next to the minimal clearance of particles from the deep lung by transport to the ciliated airways, another possible clearance route for migrating particles and particle-laden macrophages is the pulmonary lymph drainage system (Raabe, 1984). Particles that penetrate the alveolar surface can migrate through the lymphatic drainage system to pleural, hilar and tracheal lymph nodes. This migration is very slow (several months; Lippmann et al., 1980). Wright and Kuschner (1977) reported that only short fibres (< 5 μm length) were transported to hilar lymph nodes in guinea pigs after intratracheal injection. Asbestos particles eventually trapped in the pulmonary interstitium cannot be removed or redistributed mechanically (Raabe, 1984). Ultimately all uncleared material will reside in the connective tissue, and can be seen by electron microscope as mainly subpleural foci (Lippmann et al., 1980).

Wagner et al. (1974) observed a linear increase in amphibole dust retained in rat lungs with increasing cumulative inhaled dose; this linear relationship was not observed with chrysotile (2 different types), which accumulated only to a very small extent in the lungs. Directly after termination of 6 month inhalatory exposure, the lung amphibole content was approximately the same for amosite, crocidolite and anthophyllite exposed rats (4.4-4.7 mg/animal). 18 Months later, the amounts recovered from rat lungs were 1.2 and 1.3 mg/animal for amosite and crocidolite, and 2.6 mg for anthophyllite. The differences in clearance between the amphiboles were not statistically significant.

Autopsy on groups of humans with estimated high and low occupational exposure to asbestos also suggested that more amphiboles than chrysotile are retained in the lungs, because in subjects with a long time lapse between the last exposure and autopsy, amphibole fibres were recovered in larger numbers in the lungs than chrysotile fibres. The core of asbestos bodies -see 1.3.3.- also consisted mainly of amphiboles. Chrysotile, however, was more often seen in pleural plaques (= thickened pleural foci), mainly as very short fibrils. The variation in fibre content of these pleural plaques was much smaller than the variation found in lung tissue fibre content, the latter being directly related to estimated exposure. This suggests that the migration of fibres to the pleura is relatively independent of the amount of fibres

deposited in the lungs. The proportion of fibres with length < 5 μm in lung parenchyma of these humans ranged from 70% to 90% depending on exposure: heavily asbestos-exposed subjects had a larger proportion of long fibres in lung parenchyma than those with estimated low asbestos exposure. The mean fibre length of coated (see 1.3.2. and 1.3.3.) optically visible (> 5 μm) fibres found in lung parenchyma was 51, 45 and 37 μm for subjects with high, low or no estimated exposure to asbestos, respectively; uncoated fibres were generally shorter. Chrysotile in pleural plaques was found mainly as thin "ultimate" fibrils; the mean fibre length of optically visible coated fibres in the pleura was 28 μm (Sebastien et al., 1977).

Uptake in blood

Only particles with physical diameter < 10 nm can diffuse through pores in the alveolar region into the blood (Raabe, 1984), but the possibility of larger asbestos fibres directly penetrating the alveolar tissue and the vascular endothelium cannot be excluded. Griffis et al. (1983) reported the presence of crocidolite asbestos in the blood of Beagle dogs 4 days after 60 minutes inhalation of 1.5% (v/v) neutron-irradiated crocidolite in air (cumulative inhaled dose 7-10 mg). (No further details were given; the radioactivity was probably measured in arterial blood obtained after exsanguination). From the urinary excretion data of these dogs it can be estimated that 3% of the initially deposited crocidolite -or more- must have reached the bloodstream. Since a large proportion of deposited asbestos is cleared from the lungs into the GI tract (see Clearance/retention) some fibres found in blood and urine may have passed the GI barrier. Another possibility of fibres reaching the bloodstream after inhalation is via the lymphatic system.

1.2. Distribution

1.2.1. Animal studies

The overall impression is, that there is initially no preferential distribution of asbestos fibres entering the circulation to one particular type of tissue. Intravenously injected tritiated or neutron-activated chrysotile was rapidly distributed among lungs, spleen and liver of rats within 6 minutes, and decreased in the lungs and slightly increased in the liver, spleen and muscle during the next 24 hours (Cunningham and Pontefract, 1973). Although Roe et al. (1967) found highly selective distribution of 4 subcutaneously injected asbestos varieties into the serosal membranes of the

thorax and abdomen of mice, Kanazawa et al. (1970) could not confirm this in a very similar study with mice. The latter authors have carefully examined all injection sites for inadvertent injection of asbestos into abdominal or thoracic cavities; the former did not report similar safety measures, which may be one explanation for the different results. Animal tissues in which asbestos fibres were detected at some stage after oral or intragastric administration are: liver, lungs, kidney cortex, spleen, omentum, heart, brain, pancreas and lymph nodes (Bolton et al., 1982; Patel-Mandlik and Millette, 1980; Kaczenski and Hallenbeck, 1984; Cunningham and Pontefract, 1973). Shortly after single inhalation of neutron-irradiated crocidolite the liver and head (no details given) of Beagle dogs showed radioactivity (Griffis et al., 1983).

In the long term, fibres retained in tissues may be redistributed into lymph nodes and subserosal foci, as was already described for inhaled fibres in lung tissue. Kanazawa et al. (1970) showed that the migration of asbestos fibres away from the site of subcutaneous injection takes place mainly along lymphatic pathways, and some fibres could be detected in subpleural foci in longterm survivors of their study.

In all cases the reported tissue fibre concentrations were low. Fibres recovered from tissues were not consistently different in size from the administered fibres.

1.2.2. Human studies

Cunningham and Pontefract (1973) examined the tissues of 3 humans from the general population, with no history of occupational exposure to asbestos, who had died from natural causes (no other details given). They found levels of 1.1-3.8 x 10^5 chrysotile fibres /g brain, 0-2.5 x 10^5 fibres/g spleen and 7.7-9.2 x 10^5 fibres/g peritoneum. Autopsy data reported by Carter and Taylor (1980) for a group of residents from an area with high amphibole content in drinking water may not be reliable because of sample contamination (Meek, 1983).

1.2.3. Placental transport

Asbestos fibres were demonstrated to be able to cross the placenta of rats: after a chrysotile suspension in water had been injected into the femoral vein of pregnant rats at 2 day intervals beginning on the 10th to 14th day of gestation, the fibre content of foetal livers and lungs was significantly

higher in the experimental group than in the control group (Cunningham and Pontefract, 1974).

1.3. Biotransformation

1.3.1. Degradation

Ingested chrysotile fibres may be altered by contact with gastric juice and probably also with other body fluids. It was observed that magnesium (and nickel) ions leach out as a result of exposure to water for prolonged periods, to strong acids and to simulated gastric juices, leaving a magnesium-free silica network. The gross crystallinity of the fibres is thus destructed and they become more fragile. The smaller the fibre diameter, the faster this loss is (Seshan, 1983; Saxena et al., 1982). Similar degradation of fibres may also occur in lung tissue. Jaurand et al. (1984) demonstrated that leaching of Mg from chrysotile fibres occurred within rabbit alveolar macrophages and rat pleural mesothelial cells in culture. The kinetics of Mg-leaching in the macrophages resembled those in a medium of pH 4, whereas the kinetics in pleural cells resembled those in a medium of pH 7.
Furthermore, fibres of chrysotile tend to fragment longitudinally into thinner fibrils in the body (NRC, 1984). Amphibole fibres are much more resistent to both forms of degradation.

1.3.2. Coating

The surface characteristics of fibres in the body may be modified by adsorption of compounds like mucin (in the GI and higher respiratory tract) and lung surfactant (in the lower parts of the lungs), which adsorb onto the fibres and have effect on the surface charge and the leaching of magnesium, and hence reduce possible cytotoxic properties of the fibres. Complex organic compounds such as muco- and glycoproteins may do the same in the GI tract (Seshan, 1983; NRC, 1984).

1.3.3 Asbestos body formation

The formation of "asbestos bodies", which is sometimes also called coating, is an intracellular process. A fibre becomes incorporated into the intracytoplasmic vacuole (phagosome) of a macrophage or giant cell (= two or more fused macrophages) and a mucopolysaccharide matrix is deposited on the fibre. Iron accumulates in the coating initially as hemosiderin. Finally the cell dies and the yellow iron-protein coated body is released into the

pulmonary parenchyma, where it remains as biologically insignificant, probably inert matter. Occasionally, asbestos bodies are also seen in other parts of the body. Fibres with a length of less than 5-10 μm are rarely coated; since chrysotile tends to fragment more than amphiboles this is probably why the core of asbestos bodies found in the general population usually consists of amphiboles (Churg and Warnock, 1981; Rebuck and Braude, 1983). Because the core may also contain other minerals than asbestos, a more general name is "ferruginous bodies". Ferruginous bodies can be found from 3 weeks after exposure onwards (Holt, 1982).

The presence of asbestos bodies in broncheo-alveolar lavage fluid (BALF) is often used to estimate the past exposure of humans to asbestos. However, this is only a very rough estimate, which cannot be used for assessment of dose-response relations: only long fibres are coated to form bodies whereas a considerable proportion of fibres may consist of very short fibres; the ratio bodies/total fibres found in human lungs is quite variable (Sebastien et al., 1977; Churg and Warnock, 1981).

1.4. Excretion

1.4.1. Oral

Animals

The major part of asbestos recovered from the feces of rats fed 100 mg/kg chrysotile, crocidolite or amosite for 1 month was excreted within 48 hours after termination of the experiment. No more asbestos could be detected in fecal pellets after 7 days (Bolton and Davis, 1976). After 28 days, asbestos could not be detected in the intestines and intestinal contents. The urinary excretion of asbestos was not measured; however, since GI absorption was shown to be very low in rats, fecal excretion of asbestos probably covered the major part of the intake. Data on the urinary excretion of asbestos in animals after ingestion are not available.

Man

The fecal excretion of asbestos or other mineral fibres after ingestion was not studied in humans, but it can safely be assumed that the major part of ingested asbestos will be excreted in feces, like in animals, since GI absorption was very low. For people drinking water with a high amphibole content, urinary amphibole excretion was significantly higher than for people

drinking filtered or uncontaminated water but it was still very low (0.1% of total ingested amphibole). For 2 persons switching from a high to a low amphibole intake via drinking water, the urinary amphibole excretion decreased correspondingly (Cook and Ohlson, 1979). A comparable excretion pattern could not be found for chrysotile (Boatman et al., 1983; Cook and Ohlson, 1979); this may be due to contamination of control samples with chrysotile, or to equal exposure of the experimental and control groups by e.g. air and food (in which chrysotile is more common than ampbiboles). The urinary concentration of attapulgite of a woman that had received the mineral as a drug for 6 months (9000 mg/day) was 3 x 10^5 fibres/ml (Bignon et al., 1980). Using a conversion factor of 10^{10} fibres per mg asbestos (Cunningham and Pontefract, 1973) and assuming a urinary production of 1.5 l/day, it can be calculated that this is about equal to a daily urinary attapulgite excretion of 0.045 mg/day which is only 0.0005% of the daily intake.

1.4.2. Inhalation

Animals

Rats exposed to irradiated crocidolite showed a rapid and a slow phase of fecal excretion of radioactivity. The rapid phase had a halftime of 0.43 day; this obviously represented clearance of the upper part of the respiratory tract. The slow phase, possibly representing clearance of the alveolar region of the lungs via the GI tract, had a halftime of 29 days. When animals were killed 30 days after exposure, 75% of radioactivity present in the organism immediately after exposure had been excreted in the feces (Evans et al., 1973). Rats exposed to neutron-irradiated anthophyllite showed a fecal excretion of radioactive anthophyllite after 14 days amounting to 1.4%/day of the lung content. After 120 days this had fallen to 0.5% daily (Morgan et al., 1978). Beagle dogs exposed to neutron-irradiated crocidolite excreted approximately 70% of the initial body burden within 4 days after exposure. 96% Of this activity was in the feces, and therefore 4% probably in urine (Griffis et al., 1983).

Man

Humans, exposed occupationally to high, moderate and low chrysotile air concentrations, had an average fibre content in feces of 26.47 x 10^6, 11.93 x 10^6 and 0.37 x 10^6 fibres/g feces, respectively. The fibre content of the feces was thus significantly higher in higher exposure groups (Cunningham et

al., 1976). Human data on urinary excretion of fibres after inhalation were not available, although they may be important for a better quantification of the amount of inhaled fibres that reach the bloodstream and other tissues.

1.5. Summary and conclusions

Ingestion

There has been some dispute whether asbestos fibres are able to cross the gastrointestinal wall after ingestion. Rat experiments have indicated that the major part of ingested asbestos is excreted into the feces within 48 hours after ingestion (Bolton and Davis, 1976). However, a minor part of ingested, intact asbestos fibres may penetrate into the gastrointestinal wall, or cross the gastrointestinal wall and reach the bloodstream and various tissues and organs. The results of experiments with rats and baboons, investigating this passage of fibres through the gastrointestinal wall after ingestion, are difficult to evaluate. There are many possibilities of confounding contamination of tissues with asbestos, and the available analytical techniques are not very sensitive. Nevertheless, the observed time-related increase in the asbestos concentration of hepatic portal blood of rats until 7 hours after asbestos ingestion indicates that passage of fibres from the gastrointestinal tract into blood does occur (Weinzweig and Richards, 1983).

Animal tissues outside the gastrointestinal tract in which asbestos fibres have been detected after oral or intragastric administration are the liver, lungs, kidney cortex, spleen, omentum, heart, brain, pancreas and lymph nodes (Bolton et al., 1982; Patel-Mandlik and Millette, 1980; Kaczenski and Hallenbeck, 1984; Cunningham and Pontefract, 1973). There is no preference for one particular type of tissue, although there are some indications that fibres residing in the tissues are gradually redistributed towards subserosal foci and lymph nodes.

Chrysotile fibres reaching the stomach after ingestion may be partly broken down by the dissolving action of gastric juice. In the tissues, chrysotile asbestos may be similarly dissolved, or fragmented into small fibrils. In contrast, amphibole asbestos fibres are much more resistent to degradation in the body.

The quantitative recovery of ingested fibres from the various tissues was generally very low. In three independent rat studies, the maximum amount of fibres recovered per gram tissue was 10^{-11}-10^{-10}x smaller than the cumulative ingested amount of fibres per gram body weight (Bolton et al., 1982;

Cunningham et al., 1977; Gross et al., 1974). The maximum recovery rate of ingested asbestos fibres from rat lymph was also very low (Sebastien et al., 1980). The mean fibre length of fibres recovered from tissues was not consistently different from that of ingested fibres.

In humans, the uptake of ingested fibres from the gastrointestinal tract was demonstrated by recovery of fibres from urine. The urinary amphibole fibre concentration directly reflected the intake from drinking water in volunteers switching from a high to a low amphibole intake. The maximum reported urinary excretion, however, was very low (0.1% of total ingested fibres; Cook and Ohlson, 1979). Cunningham and Pontefract (1973) analysed the spleen, brain and peritoneum of three humans from the general population with no history of occupational exposure to asbestos. Although chrysotile fibres were found (in concentrations ranging from 0 to 9.2 x 10^5 fibres.gram^{-1} tissue), these cannot be related to exposure.

In conclusion, it can be stated that only a very small proportion of ingested asbestos fibres will pass the gastrointestinal wall and will be excreted into urine; only few fibres penetrate into tissues and are retained there. The major part of ingested asbestos will be excreted into the feces.

Inhalation

Two mechanisms of deposition in the respiratory tract are important for inhaled asbestos fibres: interception, which mainly depends on fibre length, and impaction, which is dependent on the mean aerodynamic equivalent fibre diameter (Dae) but relatively independent of fibre length. The Dae is approximately 3-4 x larger than the actual diameter for straight fibres (Gross, 1981). The upper limit of respirability for fibres is a Dae of 10 μm, which corresponds with an actual fibre diameter of approximately 3 μm for amphiboles, and a fibre length of 200 μm (Lee, 1985).

Particles with a large Dae and/or large fibre length, and particles with a very small Dae (< 0.1 μm), are deposited preferentially in the nasopharynx; particles with a Dae of > 2 μm are mainly deposited in the tracheobronchial region. These parts of the respiratory tract are mainly cleared via the mucociliary escalator into the gastrointestinal tract, which occurs relatively rapid (hours). Particles with a Dae between 0.1 and 2 μm are deposited almost exclusively in the alveolar region of the lungs, beyond the ciliated airways. Clearance from this region is much slower, and may take months to years (Raabe, 1984; Lippmann et al., 1980).

Most fibres with a length < 3 μm entering the alveolar region of the lungs are rapidly phagocytized by pulmonary macrophages, but free fibres may also enter cells of the epithelium, interstitium, or endothelium of capillaries. In vitro studies indicate that fibres longer than 3-5 μm may be phagocytized incompletely, with part of the fibres remaining uncovered (Beck and Tilkes, 1980). Only a small proportion of particle-containing macrophages will be transported to the ciliated airways; most macrophages, as well as free fibres, are slowly migrating towards the periphery of the lungs and to the pleura, where the asbestos fibres finally remain. Some fibres, mainly the longer ones (> 5-10 μm length), are coated and form inert asbestos bodies, but many uncoated fibres can be found in lung tissue. Both rat studies and observations in humans suggest that amphibole fibres accumulate to a larger extent in the lungs than chrysotile fibres (Wagner et al., 1974; Sebastien et al., 1977). Chrysotile fibres are probably partially dissolved, whereas amphibole fibres are not. Chrysotile may also split into thinner fibrils in lung tissue, which are not easily detected.

Studies with rats and dogs have demonstrated that a large part (70-75%) of asbestos deposited in the lungs after inhalation will be excreted in the feces. The fecal excretion of inhaled asbestos shows a rapid phase, corresponding with the rapid mucociliary clearance from the lungs into the gastrointestinal tract, and a very slow phase, which probably represents a very gradual clearance from the alveolar region of the lungs (Evans et al., 1973; Morgan et al., 1978; Griffis et al., 1983). The fecal excretion of asbestos by humans also reflects inhalatory exposure (Cunningham et al., 1976). Unfortunately, data on urinary excretion of asbestos after inhalatory exposure are not available.

Summarizing, it can be concluded that respirable asbestos particles with a Dae of 0.1-2 μm, and relatively independent of fibre length, have a high possibility of reaching the alveolar region of the lungs, where clearance is very slow. Many uncleared particles will migrate to the periphery of the lung and the pleura. Whereas chrysotile may be partly dissolved, or fragmented into smaller fibrils, amphibole fibres are probably not greatly altered during residence in lung tissue, and remain there permanently.

2. EFFECTS ON ANIMALS

2.1. Acute/shortterm toxicity

The effects of single or shortterm asbestos exposure are only of relevance in the context of longterm (fibrogenic or carcinogenic) effects and will therefore not be described under the heading of acute or shortterm toxicity.

2.2. Longterm toxicity/carcinogenicity

2.2.1. Oral studies

Noncarcinogenic effects

Jacobs et al. (1978) observed cellular damage of the mucosal lining of the rectum, colon and ileum (villi) after feeding chrysotile to rats for either 1 week or 14 months, as was indicated by increased DNA levels in the intestinal lumen. Others did not find any microscopic lesions of the GI tract of rats in either shortterm (Meek and Grasso, 1983) or longterm (e.g. Bolton et al., 1982) studies.

Some investigators studied cellular proliferation in the GI tract in rats and monkeys after single or repeated oral doses of asbestos (in comparison with the fibrotic reaction of lung tissue after inhalation) by measuring the incorporation of tritiated thymidine. Some changes of thymidine incorporation into the wall of various parts of the GI tract and in pancreas and liver were observed after various time intervals, but there was no consistent picture and definite conclusions can therefore not be drawn (Amacher et al., 1974, 1975; Epstein and Varnes, 1978; Jacobs et al., 1977; Bolton et al., 1982).

Carcinogenic effects

In a critical review Toft et al. (1984) used a scoring system to weight the results of well- and less well-designed oral carcinogenicity studies, and found no conclusive evidence that asbestos is carcinogenic to animals after ingestion. Since their evalution, some new relevant data have been published. In table 3 the available quantitative oral carcinogenicity studies with asbestos are summarized. Some available material was not included in the table for various reasons. Two studies were considered inadequate: Cunningham et al. (1977) found positive results in a study with only 10 animals, which could not be reproduced in a later study with larger groups; Gibel et al. (1976) used asbestos filter material which was not pure and could have been contaminated

with (other) carcinogens responsible for the positive effects. A "qualitative" study, in which rats reveived tap water of various origins and lake sediments with different, not very well-quantitated amounts of naturally occurring amphibole fibres, failed to show any carcinogenic effects (Hilding et al., 1981). Some studies included treatment with a known intestinal carcinogen (e.g. 1,2-dimethylhydrazine - DMH) to investigate the possible tumor-promoting or cocarcinogenic properties of asbestos, but the results cannot be properly evaluated because of the very high background tumor incidence caused by these initiating carcinogens; nevertheless, they do not suggest that asbestos is a promoter or cocarcinogen after oral exposure (NTP, 1985; McConnell et al., 1983b; Ward et al., 1980).

Some studies that were not quite up to accepted standards -with respect to the type or amount of animals used or the duration of the administration period- were included in table 3 because they are frequently referred to in literature; omission of these studies would make the remaining number of studies very small, but it would not alter the final conclusion. In the studies summarized in the table, only few statistically significant effects have been found. They will be briefly discussed below.

In hamsters receiving 1% dietary chrysotile of two different fibre sizes (shortrange and intermediate range) for lifetime, an increased incidence of primary tumors was observed in both groups which could be ascribed mainly to the increased incidence of adrenal cortical adenomas. This increase was significant only when compared with pooled controls, not with concurrent controls (McConnell et al., 1983a). However, in this study DMH, a wellknown intestinal carcinogen in rats (NTP, 1985) and also in a pilot study with hamsters (McConnell et al., 1983a), did not produce any increase in intestinal tumors either. This raises serious doubts about the suitability of the animals used in this study for the detection of GI cancers. It also has to be noted that hamsters are relatively insensitive to the effects of asbestos via other routes of exposure (NRC, 1984). In another study with hamsters (the only available study designed to find a possible dose-response relationship) 2 early squamous-cell carcinomas of the forestomach and 1 peritoneal mesothelioma were found in the mid dose group, whereas no similar tumors were seen in the high or low dose group (Smith et al., 1980, cited by IPCS, 1986). The evidence of hamster oral carcinogenicity studies can therefore be considered as negative, but hamsters may not be the most sensitive species.

In F344 rats, the incidences of C-cell carcinomas of the thyroid and of mononuclear leukemia were increased after lifetime feeding of 1% amosite, in

males only; males fed amosite for lifetime with preweaning gavage of chrysotile also had increased mononuclear leukemia, but no increased C-cell carcinomas of the thyroid (McConnell et al., 1983b). However, it must be noted that both types of tumors frequently occur in this particular strain of rat, and that the effects were not significant in females. Since the incidence of GI tumors in these studies was not different for treated and control animals, it was concluded that the observed tumors were not treatment-related.

A slight support of tumorigenic effects of ingested asbestos may be the incidental occurrence of mesotheliomas (which is normally very rare but has been demonstrated after intrapleural/intraperitoneal injection of asbestos): 1/189 mesothelioma in the abdomen was reported in F344 rats on a lifetime diet containing 10% chrysotile B (Donham et al., 1980), 1/60 peritoneal mesothelioma was described in hamsters receiving 5 mg amosite/l drinking water for lifetime (Smith et al., 1980, cited by IPCS, 1986), 1/30 pleural mesothelioma occurred in a group of rats fed asbestos (50 mg/kg b.w.) and 1/30 peritoneal mesothelioma was reported in rats fed diatomaceous earth (50 mg/kg b.w.) -which is a constituent of water filters commonly used for drinking water filtration with unknown particle structure- for lifetime (Hilding et al., 1981); mesotheliomas were not observed in any of the untreated control animals. Another type of tumor reported in 2 different studies, in asbestos- or talc[1]-treated animals, was leiomyosarcoma of the stomach (1/24 rats fed 90 mg/kg amosite for lifetime - Bolton et al., 1982; 1/32 rats fed 250 mg/kg talc for 101 days, and 1/32 rats fed 250 mg/kg superfine chrysotile for 101 days - Wagner et al., 1977). However, since these effects were far from significant, even in longterm studies with high dose levels and relatively large amounts of test animals, they cannot by themselves be considered as evidence for carcinogenicity by the oral route.

Significantly increased incidences of benign neoplasms which may be directly related to the ingestion of asbestos were reported in 2 studies in male rats fed chrysotile for lifetime. At approximately 90 mg/kg/day chrysotile A benign neoplasms were observed mainly as hemangiomas of the mesenterium (Bolton et al., 1982); at a dose of approximately 500 mg/kg/day intermediate range chrysotile benign adenomatous polyps were seen in the epithelium of the descending colon, but the incidence was significanty different only from

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1) Talc may contain traces of tremolite or actinolite asbestos.

pooled controls, not from concurrent controls (NTP, 1985). It must be noted that the overall tumor incidence was extremely high in this study (almost 100% of control as well as treated animals had primary tumors); this was not commented on in a peer review accompanying the final NTP report. Based on the latter study, the US EPA has recently concluded that there is limited evidence (namely, the occurrence of benign adenomatous polyps in the colon of rats) for carcinogenicity of asbestos of intermediate[1] but not of short[2] fibre length, whereas in drinking water only relatively short[3] fibres have been found (EPA, 1986). A significantly increased incidence of malignant neoplasms of the colon, however, was not reported in any study, not even by Donham et al. (1980), who concentrated in their study on possible malignant effects on the colon, and used an extremely high dose (10% in feed for lifetime). The biological relevance of these benign neoplasms is therefore doubtful, especially since they were only observed in males, in numbers significantly different only from pooled controls, not from concurrent controls.
In conclusion, it can be stated that the available studies do not indicate that asbestos is carcinogenic in rats and hamsters after ingestion.

2.2.2. Inhalation/intratracheal studies

Carcinogenicity, qualitative

There is sufficient evidence from experiments with rats, mice, hamsters, guinea pigs and rabbits that all asbestos types are carcinogenic in animals after inhalation (IARC, 1977), although there appear to be species differences: in rats and mice both benign and malignant tumors of the lungs are found, whereas hamsters, guinea pigs and rabbits seem to develop only benign neoplasms in the lungs (NRC, 1984). The types of tumors most often associated with asbestos exposure in rats and mice are adenomas, adenocarcinomas and squamous-cell carcinomas of the lung. (For the following quantitative evaluation of carcinogenicity, only the malignant tumors were considered). In addition to the above mentioned tumor types, mesotheliomas of the pleura are frequently noted; mesotheliomas of the peritoneum are also seen

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1) ± 60% fibres > 5 μm length; maximum length 780 μm

2) ± 20% fibres > 5 μm length; maximum length 51 μm

3) average length 0.8-4.3 μm; maximum length 80 μm

occasionally. The increase in mesotheliomas is often not statistically significant, but it is a very rare type of tumor that is almost exclusively associated with asbestos, both in humans and in animals (see 2.2.3 and 3.). Animal experiments do not confirm the observations from epidemiological studies that the GI tract is involved in asbestos-related carcinogenesis after inhalation.

Carcinogenicity, quantitative

- Mass concentration-response relationship.
  Davis et al. (1978) demonstrated that the frequency of lung tumors in rats from asbestos inhalation was concentration- related: 2 mg/m^3 chrysotile for 1 year caused 5% lung tumors (1/42 adenocarcinoma, 1/42 squamous carcinoma), whereas 10 mg/m^3 caused 20% lung tumors (6/40 adenocarcinomas, 2/40 squamous carcinomas). None of the other animal inhalation studies were designed to find a concentration-response relationship: only one asbestos concentration was studied at a time. If the different studies are compared with each other, a clear relationship between the mass concentration of asbestos in air and tumor incidence seems to be absent (see table 4). This may partly be due to a different fibre count per weigth unit of the asbestos varieties used in different studies. This will be discussed in the following paragraph.
- Fibre concentration-response relationship.
  The asbestos used in animal experiments is sometimes milled, which causes a reduction of the number of fibres detectable by light microscope (> 5 μm length) and an increase in submicroscopic fibres and in nonfibrous dust. Besides, Davis et al. (1978) observed that concentrations of more than 10 mg/m^3 asbestos in air may produce unrespirable flocs. These observations illustrate that similar mass concentrations asbestos may give very different fibre concentrations (see table 5). In table 5 the carcinogenic effects of asbestos are related to fibre concentration (rather than mass concentration) in air.
  At levels of 5.5 and 4.3 x 10^6 f/l, very similar to the level of 3.9 x 10^6 f/l for chrysotile, amosite and crocidolite produced 0/43 and 1/43 lung tumors and no mesotheliomas, whereas chrysotile produced 2/42 lung tumors and 1/42 mesothelioma in rats after 1 year inhalation (Davis et al., 1978). In the study of Reeves et al. (1974), the frequency of tumors of the lungs and pleura produced by chrysotile (7%) was very similar to that caused by crocidolite and amosite (7-9%), but at a 15-20 x lower fibre level. These

results show that differences in fibre concentration alone between comparable inhalation studies with asbestos can apparently not account for the observed differences in carcinogenicity; as intrapleural/intraperitoneal studies have indicated, fibre size may also play a role (see 2.2.3.). This will be discussed in the following paragraph.

- Fibre size.

  Both studies discussed above suggest that chrysotile is a more potent inhalatory carcinogen than the amphiboles. However, chrysotile in the study of Davis et al. (1978) had a much higher proportion of longer fibres than crocidolite and amosite (> 5 μm: 35% versus 15-18%; > 20 μm: 5% versus 0.3-0.5%). (Reeves et al. did not report the fibre sizes of the asbestos used). Recent experiment of Davis et al. (IARC, 1987; IPCS, 1986) showed that one particular type of asbestos with different fibre size may give a completely different response after inhalation: of two amosite varieties with different fibre size distribution (30% and 1% fibres > 5 μm length), tested by inhalation in rats, the variety with the longer fibres produced significantly more lung tumors than the shorter variety (> 30% and 0 lung tumors, respectively). Very similar observations were made with chrysotile. These data confirm the results from many intrapleural and intraperitoneal studies with asbestos and other fibrous materials that long fibres have a larger carcinogenic potency than short fibres (see 2.2.3.). The length of inhaled fibres is obviously very important in carcinogenicity. In inhalation studies, less attention was paid to fibre diameter than to length, but intraperitoneal and intrapleural studies indicate that fibre diameter is also important (see 2.2.3.). A comparison between different asbestos types with respect to their carcinogenic potency cannot be made without a proper fibre characterization.

- Time-response relationship.

  Wagner et al. (1974) found an approximately linear relationship between the duration of exposure to one particular type -and concentration- of asbestos and the incidence of lung tumors in rats. Data are summarized in table 6. For mesotheliomas, this relationship with the duration of asbestos exposure is probably not linear: two mesotheliomas could be found in groups of 49 rats exposed for only 1 day to crocidolite and amosite, respectively, after 1 year. This is in accordance with the observations from human occupational studies, in which mesotheliomas appear to be exponentially related to the time from first exposure (see 3.2.1.).

- Intermittent versus more continuous exposure.

Davis et al. (1980) investigated possible differences in the responses of rats exposed for 1 year to either intermittent high "peak" concentrations or more continuous "even" concentrations of chrysotile and amosite, with all groups ultimately receiving the same cumulative fibre dose. They found no significant differences in tumor incidence between the groups: However, the incidence of lung tumors observed in all groups was probably not high enough to find statistical significance. Details are given in table 7.

Carcinogenicity, synergistic effects

A strong synergistic effect of asbestos and cigarette smoke, which has been reported in epidemiologic studies with asbestos workers (see 3.2.1), could be reproduced in intratracheal studies with rats: combined intratracheal treatment of rats with asbestos and cigarette smoke or chemical carcinogens such as polycyclic aromatic hydrocarbons caused a more than additional increase in lung tumors compared to treatment with those chemicals alone (NRC, 1984; Shabad et al., 1974). Similar findings were reported for dogs (IPCS, 1986).

It has been suggested that carcinogens bind to the surface of asbestos fibres and thus have an easier access to cells: chrysotile, for example, has been demonstrated to bind a range of environmental carcinogens more strongly than other asbestos and nonasbestos fibres (Harvey et al., 1984). It is also possible that inhalation of chemicals and cigarette smoke alters the deposition, clearance and/or retention of fibres in the respiratory tract (see 1.1.3.).

Carcinogenicity, non-asbestos fibers

Recent results of a rat inhalation study with erionite from Oregon have shown that this non-asbestos fibrous mineral is extremely potent in causing pleural mesotheliomas (in 27 out of 28 animals still alive after after 12 months inhalation), whereas crocidolite of very similar fibre length distribution (53-56% of fibres > 5 μm length; 0.5-0.8% > 20 μm) and a larger fibre concentration in air (1.6×10^6 f/l versus 3.5×10^5 f/l) did not produce any mesotheliomas and only 1/28 adenocarcinoma. The proportion of very thin fibres (diameter < 0.2 μm), especially of those fibres < 10 μm length, was significantly higher for erionite (42% versus 22% for crocidolite), which may be a possible explanation for the very high potency to induce mesotheliomas. In a group rats treated with synthetic "nonfibrous" erionite, 1/28 pleural mesothelioma and 1/28 adenocarcinoma were found, which suggests that other

mechanisms not related to the fibrous structure may also play a role (Wagner et al., 1985). However, it cannot be completely excluded that the nonfibrous mineral contained a small number of biologically active fibres.
Preliminary results (reported directly after termination of exposure) with the asbestiform minerals attapulgite, with approximately 1% fibres > 5 μm length, and sepiolite, with 100% fibres < 5 μm length, suggest that these minerals are not carcinogenic in rats after inhalation for 1 year; however, definite results have not yet been published. The variety of attapulgite -but not of sepiolite- that was used did produce mesotheliomas in rats after intrapleural injection (see 2.2.3.; Wagner, 1982).
Several types of man-made mineral fibres (MMMF) like glass wool, rock wool and glass microfibres were also tested in animal inhalation studies; although some varieties had fibre sizes similar to the concurrently tested asbestos types, and some were able to produce small amounts of lung tumors, MMMF generally produced less tumors than the positive control samples of asbestos. (NRC, 1984; Wagner, 1982). It was suggested that this may be a matter of solubility. Asbestos fibres have a very low solubility, whereas fibrous glass, for example, may be more or less solubilized after prolonged stay in the lungs, depending on the variety. However, the fibre concentrations of asbestos and MMMF in the indicated studies were not always comparable and a quantitative comparison is therefore not allowed.

Fibrogenicity, qualitative

The earliest lesion reported in relation to asbestos inhalation was the occurrence of a characteristic type of fibrosis of the lungs, also called asbestosis. The most important inhalation and intratracheal studies concerning asbestosis are summarized in the tables 8 and 9; some features will be briefly discussed below.
Asbestosis has been reported to occur in all animal species after inhalatory or intratracheal exposure to asbestos (rats, mice, guinea pigs, hamsters, rabbits, gerbils, monkeys, sheep) although the degree of asbestosis may vary for different species (Reeves et al., 1974; Wagner, 1963; Wehner et al., 1979; Begin et al., 1982, 1983).
The initial event in asbestosis is the mobilization of pulmonary macrophages and polymorphonuclear leukocytes in areas of the lungs where asbestos fibres accumulate, which may partly be caused by the release of chemotactic factors by macrophages that have phagocytosed asbestos fibres and are destructed by a cytotoxic action of the fibres (Le Maho et al., 1984). The macrophages and

leukocytes aggregate initially in and around the terminal bronchioles, giving an inflammation-like reaction; the deposits become enmeshed in a fibrin network that is gradually replaced by collagen (Davis et al., 1978; Wagner et al., 1974). There is a shift from the presence of mainly type I cells towards a larger proportion of granular pneumocytes (type II cells) in the alveolar epithelium. The bronchiolar and alveolar walls thus become thickened. This type of lesion, which may be considered to be the first stage of asbestosis, was called "peribronchiolar fibrosis" by Davis et al. (1978).

At a later stage (months after first exposure to asbestos), fibrotic reactions expand to other parts of the lungs, and the diffuse focal fibrosis of the lung interstitium ("interstitial fibrosis") and of the pleura, which are characteristic of asbestosis, become manifest. In time, partial or sometimes complete obstruction of the small airways with consequent decreased lung capacity results (Begin et al., 1982, 1983; Glassroth et al., 1984). Some authors reported the occurrence of small foci of calcium phosphate accumulation ("microcalcifications") in the interstitium of rats after chrysotile -but not crocidolite- inhalation (Brody and Hill, 1982; Ogisho et al., 1984). Calcification is a well-known response to toxic interactions with cell membranes; it has been suggested that the positively charged Mg-ion of chrysotile fibres causes such an interaction (Brody and Hill, 1982), and also that membrane damage is caused by adsorption of cell membranes onto the fibres rather than by Mg-interaction (Jaurand et al., 1983; see also 2.5.). The formation of pleural calcified plaques, which is frequently described for asbestos workers, has not been reported to occur in laboratory animals (NRC, 1984).

As described in the chapter Chemobiokinetics and Metabolism (1.1.3.), most fibres retained in the lungs will move from the terminal bronchioli towards the the periphery of the lungs, into the interstitium and pleura, and remain there. This is possibly the reason why interstitial fibrosis develops only slowly and can still be seen progressing in rats 1-1.5 years after termination of exposure, whereas peribronchiolar fibrosis does not develop any further or is even regressing with time (Wagner et al., 1974; Davis et al., 1978). Several authors reported a reduced lifespan in animals with asbestosis; animals dying before termination of an experiment usually had more severe asbestosis than animals sacrificed at similar time intervals. It can therefore be concluded that asbestosis is an irreversibly progressing disease.

Fibrogenicity, quantitative

- Dose-response relationship/fibre size.

  Chrysotile, crocidolite and a synthetic amphibole with only a small proportion of fibres > 5 μm length did not produce any asbestosis in rats and guinea pigs, whereas the same asbestos type with a large proportion of fibres > 5 μm length caused significant fibrotic reactions after 1-8 intratracheal instillations (see table 9). Inhalation studies with various asbestos types in rats and mice gave similar results, with more and longer fibres producing more severe asbestosis (Davis et al., 1978; Reeves et al., 1974; Davis, cited by IPCS, 1986). Like in carcinogenicity, the degree of asbestosis therefore seems to be directly related to fibre size and fibre concentration.

- Time- response relationship.

  The degree of asbestosis in rats was demonstrated to have a positive correlation with the duration of inhalatory exposure to asbestos (Wagner et al., 1974). However, the disease also progresses after termination of exposure. Both effects are illustrated in fig. 1 (Wagner et al., 1974). Brody and Hill (1981, 1982) observed a distinct pulmonary reaction in rats after only 1 hour inhalation of 15 mg/m^3 chrysotile (3% fibres > 20 μm length), at various time points up to 1 month after inhalation. The observations included macrophage induction and aggregation, thickened alveolar duct walls and interstitial calcifications. The earliest reported observation in animal experiments of fibrin formation was already 2 hours after single intratracheal injection of amosite in guinea pigs (Dodson et al., 1983). Many other intratracheal studies also showed serious fibrotic lesions at some time point after one single intillation. These observations implicate that the time since first exposure to asbestos may be just as important for the observed degree of lung fibrosis as the duration of exposure.

- Intermittent versus continuous exposure.

  1 Year inhalatory exposure of rats to high peak concentrations of chrysotile and amosite (10 and 50 mg/m^3, respectively, for 1 day/week) resulted in an approximately 2x higher degree of interstitial fibrosis 17 months after termination of exposure than even exposure to lower doses (2 and 10 mg/m^3, respectively, for 5 days/week; peribronchiolar fibrosis was also different for the different exposure regimens, but not consistently). Thus, inhalation of high asbestos concentrations at separate occasions may produce more severe asbestosis than more continuous inhalation of lower concentrations if

the cumulative inhaled concentrations are similar (Davis et al., 1980). This is in line with the observations made earlier concerning time-response relationships.

Fibrogenicity, no-effect level

The lowest asbestos concentration studied in animals (1 mg/m^3 chrysotile, with 99% fibres shorter than 5 μm ; concentration of fibres longer than 5 μm: 3000 f/l), inhaled for 18 months did not cause any fibrotic reactions in rats (Platek et al., 1985). However, the same mass concentration with a slightly higher concentration of fibres longer than 5 μm (1.3×10^4 f/l) did cause minimal fibrosis in hamsters after 15 months inhalation (Wehner, cited by IPCS 1986). In the latter study, no indication was given of fibre size.

Fibrogenicity, non-asbestos fibers

Inhalatory exposure of rats to the asbestiform mineral attapulgite caused lung fibrosis to the same degree as crocidolite (Wagner, 1982; preliminary results, no other details given). The degree of fibrosis did not seem to be significantly different at 3, 6 and 12 months exposure for any of the fibres tested; it is not known whether fibrosis proceeded after termination of exposure.

Italian talc[1] caused fibrosis in rats to a similar degree as SFA chrysotile after inhalation for 1 year (Wagner et al., 1977); however, the amount and size distribution of fibres were not given.

In a study comparing the pulmonary response of rats to chrysotile and various man-made mineral fibres (MMMF), all tested MMMF gave some degree of fibrosis although the response was higher for chrysotile at all time intervals. However, the reaction with chrysotile was more severe after 12 months exposure than after 3 months, whereas the MMMF gave very little change with time (Wagner, 1982).

In another study, comparing amosite and various types of MMMF, the pulmonary response including fibrosis was generally much higher in the amosite group. Nevertheless, the response to MMMF appeared to be dose-related (Lee et al., 1981).

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1) Talc may contain tremolite or actinolite asbestos.

Summarizing, it can be concluded that the results obtained so far with non-asbestos fibres indicate that many non-asbestos fibres are able to induce a dose-related fibrogenic response after inhalation or intratracheal instillation, to a similar or lesser degree than the various asbestos types, depending on the material. There are some indications that fibrosis induced by MMMF is not progressive.

2.2.3. Intraperitoneal/intrapleural studies

Carcinogenicity

Intraperitoneal and intrapleural studies with asbestos and related compounds have mainly been conducted to investigate the importance of fibre size and shape in the induction of mesotheliomas. The most important information has been provided by 3 groups of investigators: Pott et al., Stanton et al., and Wagner et al., each using different techniques but arriving at basically the same conclusions. Pott et al. injected compounds into the peritoneal cavity of rats. Stanton et al. used glass pledgets containing various compounds embedded in gelatin, which they implanted in rats onto the pleural surface. Wagner et al. used an intrapleural inoculation technique, also with rats.

All 3 groups studied different asbestos types and varieties as well as many other fibrous and granular materials of different sizes. (Fibrous: consisting of needle-like particles with an aspect ratio of > 3:1; granular: consisting of particles with a rounded or amorphous structure). Almost any fibrous material studied had the ability to cause pleural or peritoneal mesotheliomas; granular materials usually had not. A list of fibrous materials that have been reported to produce malignant neoplasms upon intraperitoneal/intrapleural injection or implantation is given in table 10. Asbestos and glass fibre varieties milled or ground to yield shorter fibres invariably resulted in a lower mesothelioma incidence than intact fibres of the same material. The durability of the material was also of some importance: fibrous gypsum, for example, which is highly soluble, did not induce mesotheliomas (Pott and Friedrichs, 1972-cited by IPCS, 1986; Pott et al., 1974a,b; Pott et al., 1976; Pott, 1978; Pott et al., 1986; Stanton and Wrench, 1972; Stanton et al., 1977; Stanton and Layard, 1978-cited by IPCS, 1986; Stanton et al., 1981; Wagner et al., 1973; Wagner et al., 1977; Wagner, 1982; Wagner et al., 1982; Wagner et al., 1984).

Wagner et al. reported a strong relationship between the number of fibres > 5 μm length in inoculated samples and the induction of mesotheliomas in rats

after intrapleural injection. The limit of 5 μm is often used for practical reasons to characterize an asbestos sample, since it is the detection limit of fibres countable by light microscope. However, in these experiments all fibres were counted and characterized very precisely by electron microscope; the length of approximately 5 μm nevertheless appeared to be critical for biological activity. Based on an extensive set of experiments, this group tends to consider fibrous samples consisting exclusively of fibres < 5 μm length as having no carcinogenic potency. In a recent experiment by this group, 2 samples of crocidolite, milled for several hours to yield short fibres, caused 13-15% mesotheliomas, although no fibres > 6.5 μm appeared to be present in the inoculum. Upon the detection of longer fibres in the lungs of exposed animals, the inoculum was carefully reexamined, and some fibres in the longer size range were discovered after all (Wagner et al., 1984). The authors ascribed the mesotheliomas to this small fraction of longer fibres; however, it cannot be excluded that smaller fibres were at least partly responsible for the observed effects.

Stanton et al. statistically correlated tumor probability in their experimental model with the number of fibres present in different fibre size categories. Initially, they did so for 17 different glass fibre varieties (Stanton et al., 1977). These experiments seemed to indicate two fibre size categories associated with a high tumor probability: > 8 μm length (which agrees well with the suggested minimal active fibre length of Wagner et al.) and < 1.5 μm diameter. However, Bertrand and Pezerat (1980) elaborated these results and concluded that it was not allowed statistically to separate fibre length and diameter; tumor probability rather seemed to be a continuous, increasing function of the aspect ratio (length:diameter). Extension of the experiments of Stanton et al. to 72 varieties of asbestos, glass fibre and other materials confirmed this: thin fibres shorter than 8 μm and, to a lesser extent, long fibres thicker than 1.5 μm also had a positive correlation with tumor probability. However, statistical correlations should always be interpreted with great care. The correlation data of tumor probability and fibre size in these experiments are presented in table 11 (Stanton et al., 1981).

Pott et al. also developed a hypothesis, based largely on their own experiments. This hypothesis is illustrated in fig. 2. A fibre with length 20 μm or more and diameter 0.1-0.25 μm is considered to have the highest relative carcinogenic potency (100%), which decreases with a decreasing length and/or an increasing diameter (Pott, 1978). The results of Stanton et al. fit in

remarkably well with this hypothesis. The main difference between this theory and that of Wagner et al. is the absence of a narrow definition of a fibre size that determines whether a fibre is biologically active or not; the carcinogenic potential is rather considered to be a continuous function of fibre size. Fig. 2 demonstrates that, at similar fibre concentrations, the risk calculated by Pott et al. from fibres < 5 μm length will indeed be only a fraction of the risk from longer fibres; at high fibre concentrations however, the carcinogenic potency of short fibres might be considerable.

A decreased intrapleural/intraperitoneal carcinogenic potency was reported for chrysotile from which 80% or more Mg had been removed by acid treatment ("acid-leaching"; Morgan et al., 1977; Monchaux et al., 1981). It is uncertain whether this is caused by changes in fibre size or number (splitting), chemical modification, or other factors (IPCS, 1986). However, although chrysotile in the body may be similarly leached, there is no evidence that chrysotile has a lower carcinogenic potency than other asbestos types: some intraperitoneal/intrapleural studies did indicate a lower, some a higher tumor probablility for chrysotile, others indicated no differences between the asbestos types; in most cases the fibre size distribution was not given, which makes a proper comparison impossible (IPCS, 1986).

Modified chrysotile (treated with $POCl_3$ at high temteratures) also had a lower carcinogenic potency than normal chrysotile after intraperitoneal injection (Maltoni, IARC, 1987).

Fibrogenicity

The results of intrapleural and intraperitoneal studies confirm those of inhalation experiments: shorter fibres, both asbestos and nonasbestos, are less fibrogenic than longer fibres of the same material (NRC, 1984; IPCS, 1986). However, investigations concerning the more precise fibre sizes causing fibrosis are not as extensive as for carcinogenesis. Some investigators believe that asbestos-related lung cancer is always preceeded by a fibrotic condition of the lung (Kuschner, 1982; 1986), others feel that both conditions may exist independently (WHO, 1986). Despite the similarity in the fiber sizes that are apparently involved in carcinogenicity and fibrogenicity, there is as yet no evidence from animal experiments that both processes are directly related.

2.2.4. Summary and conclusions

Oral studies

There are no indications that asbestos causes serious effects in rats after either shortterm or longterm ingestion (Meek and Grasso, 1983; Bolton et al., 1982). The only observed noncarcinogenic effect, which was noted in only a few of the performed studies, was minor cellular damage of the mucosal lining of the gastrointestinal tract (Jacobs et al., 1978; Amacher et al., 1974, 1975; Epstein and Varnes, 1978).

Of the available oral animal carcinogenicity studies with asbestos, many were not quite up to accepted standards. In the studies which were considered adequate, only few statistically significant effects were found, in F344 rats and in Syrian hamsters.

In F344 rats, 1% dietary amosite for lifetime caused an increased incidence of C-cell carcinomas of the thyroid and of mononuclear leukemia, but in males only, and no increased gastrointestinal tumors were observed. The indicated tumor types often occur in this strain (McConnell et al., 1983b). 1% Dietary chrysotile with intermediate range fibres caused an increased incidence of benign neoplasms of the colon after lifetime ingestion. However, in another study, 10% of the same asbestos type in feed did not cause any increase in benign or malignant tumors of the colon (Donham et al., 1980); besides, the benign neoplasms were only observed in males, and were only significant when compared with pooled controls (NTP, 1985). 1% Dietary chrysotile with shortrange fibres and 1% dietary tremolite did not cause any increased tumor incidence after lifetime ingestion (McConnell et al., 1983b; NTP, 1985).

In Syrian hamsters, 1% dietary chrysotile for lifetime caused an increased incidence of adrenal cortical adenomas, but in males only, and no increased gastrointestinal tumors were observed (McConnell et al., 1983a).

Occasionally reported peritoneal mesotheliomas may be suggestive of a carcinogenic effect of ingested asbestos, since this is a very rare type of tumor which has been associated with asbestos in intraperitoneal studies; however, they cannot by themselves be considered as evidence of carcinogenicity.

Treatment of rats and hamsters with known intestinal animal carcinogens in addition to asbestos feeding did not suggest that asbestos is a promoter or cocarcinogen after oral exposure (McConnell et al., 1983a,b; NTP, 1985; Ward et al., 1980).

Summarizing, it can be stated that the available animal feeding studies with asbestos do not demonstrate an increased risk of gastrointestinal tumors in rats and hamsters after ingestion. Other tumors that were sometimes slightly increased were usually also found in untreated animals, and were not increased in other comparable studies; they are therefore not considered to be treatment-related.

Inhalation/intratracheal studies

There is sufficient evidence from experiments with rats, mice, hamsters, guinea pigs and rabbits that all asbestos types are carcinogenic in animals after inhalation (IARC, 1977). The types of tumors most often associated with asbestos exposure in rats and mice are adenomas, adenocarcinomas and squamous-cell carcinomas of the lung, mesotheliomas of the pleura, and occasionally, mesotheliomas of the peritoneum. Animal experiments do not confirm the observations from epidemiological studies that the gastrointestinal tract is involved in asbestos-related carcinogenesis after inhalation.

Important quantitative information was provided by Davis et al. (1978, 1980, IARC, 1987), Reeves et al. (1974), Wagner et al. (1974), and a recent review by the IPCS (1986). Based on this information, the following statements can be made.

- The lung cancer incidence in rats resulting from asbestos inhalation is approximately linearly related to the fibre concentration in air, and to the duration of exposure.
- Mesotheliomas, however, are observed relatively frequently among rats exposed either to low asbestos concentrations, or for only short periods of time (after a long latency period). This suggests that a linear exposure-response relationship is less likely for mesotheliomas. This is in accordance with the observations from human occupational studies, in which mesotheliomas appear to be approximately linearly related to fibre concentration, but exponentially related to the time from first exposure (see 3.2.1.).
- Fibre length, and possibly also fibre diameter, are very important for carcinogenic effects after inhalation, with longer and thinner fibres producing more tumors than shorter and thicker fibres; the different asbestos types can only be compared for their carcinogenic potency after a proper fibre characterization.
- In addition to fibre size and concentration, the durability of fibres may be important. This was indicated by inhalation experiments with manmade mineral

fibres, which were sometimes also able to produce small numbers of lung tumors in rats (NRC, 1984; Wagner, 1982). Chrysotile has been reported to dissolve slowly in the body whereas amphiboles remain intact; however, despite these differences in biological solubility there are no clear indications from animal inhalation experiments that chrysotile has a lower carcinogenic potency than other asbestos types with similar fibre dimensions (see also 5.).

Intratracheal studies with rats have demonstrated a strong synergistic effect of asbestos and cigarette smoke, and of asbestos and chemical carcinogens such as polycyclic aromatic hydrocarbons, in the production of lung tumors but not of mesotheliomas (Shabad et al., 1974; NRC, 1984; IPCS, 1986).

Asbestosis is a characteristic fibrosis of the lungs, which begins as an inflammation-like reaction in and around the terminal bronchioles where fibre-containing macrophages aggregate, and gradually progresses into a diffuse focal fibrosis of the lung interstitium and the pleura. Severe asbestosis causes decreased lung capacity and partial or sometimes even complete obstruction of airways (Begin et al., 1983; Glassroth et al., 1984). This fibrosis develops slowly, but is irreversibly progressing, often even after termination of exposure.

Asbestosis has been reported to occur in all animal species after inhalatory exposure to asbestos (shortterm as well as longterm), and after single or repeated intratracheal asbestos instillation (Reeves et al., 1974; Wagner, 1963; Wehner et al., 1979; Begin et al., 1982, 1983).

As in carcinogenesis, more and longer fibres appear to produce more severe asbestosis (Davis et al., 1978; Reeves et al., 1974; IPCS, 1986). The time from onset of exposure and the duration of exposure are both important factors determining the degree of asbestosis that can be observed in rats (Wagner et al., 1974). Inhalation of high asbestos concentrations at separate occasions may produce more severe asbestosis than more continuous inhalation of lower concentrations, despite similarities in cumulative concentration (Davis et al., 1980).

Nonasbestos fibres may also produce asbestosis in rats. They usually give a lower response than asbestos in similar mass concentrations, but the response appears to be concentration- related (Lee et al., 1981; Wagner, 1982).

The lowest asbestos concentration studied in animals (1 $mg.m^{-3}$ chrysotile, with 99% fibres shorter than 5 μm ; concentration of fibres longer than 5 μm: 3000 $f.l^{-1}$), inhaled for 18 months did not cause any fibrotic reactions in rats

(Platek et al., 1985). However, the same mass concentration with a slightly higher concentration of fibres longer than 5 μm ($1.3x10^4 f.1^{-1}$) did cause minimal fibrosis in hamsters after 15 months inhalation (Wehner, cited by IPCS 1986). In the latter study, no indication was given of fibre size distribution.

Intrapleural/intraperitoneal studies

Intraperitoneal and intrapleural studies with asbestos and related compounds have mainly been conducted to investigate the importance of fibre size and shape in the induction of mesotheliomas. Three different groups of investigators arrived at basically the same conclusions. Mesotheliomas could be induced in rats by a variety of durable fibrous materials including asbestos by these routes. The tumor probability seems to be a continuous function of both fibre length and fibre diameter, and is relatively independent of the type of material. Fibres with a length of 20 μm or more and diameter 0.1-0.25 μm probably have the highest relative carcinogenic potency, which decreases with a decreasing length and/or an increasing diameter. The risk of fibres with a length of < 5 μm, and of fibres with a diameter of > 2 μm, which may still have some carcinogenic potency (Pott, 1978; Stanton et al., 1981), is assumed to be zero by many investigators (Wagner et al., 1973; Wagner, 1982) and will in any case be negligible in practice.

There are no indications from intrapleural and intaperitoneal studies that chrysotile and the amphiboles differ in carcinogenic potency. However, chrysotile from which more than 80% Mg had been removed by acid treatment (simulating the leaching of chrysotile fibres in the body) had a reduced carcinogenic potency in rats after intrapleural inoculation (Monchaux et al., 1981).

Modified chrysotile (treated with $POCl_3$ at high temteratures) also had a lower carcinogenic potency than normal chrysotile after intraperitoneal injection (Maltoni, IARC, 1987).

The results of intrapleural and intraperitoneal studies confirm those of inhalation experiments with respect to asbestosis: shorter fibres, both asbestos and nonasbestos, are less fibrogenic than longer fibres of the same material (NRC, 1984; IPCS, 1986). However, investigations concerning the more precise fibre sizes causing fibrosis are not as extensive as for carcinogenesis. Some investigators suggest that asbestos-related lung cancer is always preceeded by a fibrotic condition of the lung (Kuschner, 1982;

1986), others believe that both conditions may exist independently (WHO, 1986). Despite the similarity in the fibre sizes that are apparently involved in carcinogenicity and fibrogenicity, there is as yet no evidence from animal experiments that both processes are directly related.

2.3. Reproduction/teratogenicity

Although asbestos has been demonstrated to cross the placenta of rats after intravenous injection (see 1.2.3.), only one study -with mice- concerning possible effects of asbestos on embryonic development has been published. Pregnant mice reveived 1.43, 14.3 or 143 μg/ml chrysotile in drinking water (approximately 0.4, 4 or 40 mg/kg b.w./day) from days 1 to 15 of pregnancy, and were sacrificed at day 18. No maternal effects were observed in any of the groups; the average number of implants was slightly lower for the lowest dosage group, which was not considered to be treatment-related; no effects were observed for any of the other measured parameters (average numbers of resorptions and fetuses, fetal weight, malformations and developmental disturbances -Schneider and Maurer, 1977).

In vitro exposure of mouse blastocytes to 1, 10 or 100 μg/ml chrysotile did not affect the development of the blastula in vitro; however, after implantation of exposed blastula into recipients, a dose-related increase in dead and resorbed fetuses was noted. Fetal weigth, growth and development were not affected. Electron microscopic examination of intact blastula and blastula with removed zona pellucida showed that the zona pellucida effectively protected the blastula from fibre penetration (Schneider and Maurer, 1977).

2.3.1. Summary and conclusions

Although asbestos has been demonstrated to cross the placenta of rats after intravenous injection, only one study concerning possible effects of asbestos on embryonic development has been published. The average number of implants in mice receiving approximately 0.4, 4 or 40 $mg.kg^{-1}$ b.w. chrysotile daily in drinking water during pregnancy was slightly lower for the lowest dosage group, which was not considered to be treatment-related; no other effects were observed. In vitro exposure of mouse blastocytes to 1, 10 or 100 $\mu g.ml^{-1}$ chrysotile did not affect the development of the blastula in vitro but caused a dose-related increase in dead and resorbed fetuses after implantation (Schneider and Maurer, 1977).

2.4. Mutagenicity

2.4.1. Bacterial systems

Chrysotile, crocidolite, amosite and anthophyllite were not mutagenic in the Ames test with Salmonella typhimurium and in Escherichia coli, either with or without metabolic activation (Chamberlain and Tarmy, 1977; Szyba and Lange, 1981). Fibrous Richterite, a natural alkali-rich analogue of tremolite, caused a significantly increased mutation frequency in a reverse mutation test with E. coli CSH50. However, metabolic activation increased the mutagenic activity, whereas the durable fibres are very unlikely to be changed by enzymatic processes; it was therefore assumed that an unknown mutagen was introduced along with the unpurified Richterite sample (Cleveland, 1984).

2.4.2. In vitro mammalian systems

One group of investigators reported a weak mutagenic activity of chrysotile, crocidolite and amosite at the HPRT-locus in Chinese hamster lung cells in culture (at 10 $\mu g/cm^2$)[1]. Mutations were restricted to cells containing asbestos dust, containing cells from other cells by gravitational settling (Huang et al., 1978; Huang, 1979). The effects may therefore have been secondary to cytotoxicity (IARC, 1982), or to increased permeability allowing other mutagens into the cells (Newman et al., 1980, cited by EPA, 1985). The mutagenic action of asbestos at this locus could not be confirmed by other investigators at lower dose levels of 0.1-2 $\mu g/cm^2$ in Syrian hamster embryo (SHE) cells and rat epithelial cells (Newman et al., 1980, cited by EPA, 1985; Oshimura et al., 1984; Reiss et al., 1982, 1983). Mutagenicity at the Na^+-K^+-ATPase locus of SHE cells was also absent after exposure to 1-2 $\mu g/cm^2$ chrysotile or crocidolite in vitro (Oshimura et al., 1984).

Dose-related increases in chomosomal aberrations were reported by various authors, for all examined asbestos types, in SHE cells, Chinese hamster lung cells, Chinese hamster ovary (CHO) cells and human blood lymphocytes in culture. Both structural and numerical changes were noted. Breaks, gaps, fragments, aneuploidy and polyploidy were the changes reported most frequently; dicentrics and exchanges were sometimes also noted (Hesterberg and

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1) Concentrations were expressed as $\mu g/cm^2$ of culture dish, because the asbestos particles settled to the bottom within 1 hour after addition of the suspension.

Barrett, 1985; Huang et al., 1978; Lavappa et al., 1975; Oshimura et al., 1984; Price-Jones et al., 1980; Sincock and Seabrigth, 1975; Sincock, 1977, cited by EPA, 1985; Valerio et al., 1983). Hesterberg and Barrett (1985) observed asbestos fibres within mitotic cells, interacting directly with the chromosomes; it was proposed that this physical interaction of asbestos with chromosomes or with structural proteins of the spindle apparatus might be responsible for structural and numerical changes. In contrast, chromosomal aberrations were not observed in human primary fibroblasts and human lymphoblastoid cells after in vitro exposure to chrysotile and crocidolite, in concentrations similar to those used for CHO cells (10 $\mu g/cm^2$; Sincock et al., 1982).

2.4.3. In vivo mammalian systems

Single oral or intraperitoneal administration of different doses of chrysotile (0.4-400 mg/kg b.w.) did not increase the freqency of micronuclei in bone marrow cells of mice; single oral gavage of 100 or 500 mg/kg b.w. chrysotile did not increase the frequency of chromosome aberrations in bone marrow cells of monkeys (Lavappa et al., 1975). Other in vivo mammalian tests were not reported.

2.4.4. Indicator tests

In vitro mammalian systems

Results of sister chromatid exchange (SCE) assays were equivocal: Livingston et al. (1980) reported a significantly elevated SCE rate in CHO cells exposed to 10 $\mu g/ml$ crocidolite; amosite was less effective; larger chromosomes (> 5 μm) were more sensitive to this effect than shorter ones. Casey (1983) did not observe any increase in SCE rate in CHO-K1 cells, nor in human fibroblasts and human lymphoblastoid cells, at 1-50 $\mu g/ml$ crocidolite, chrysotile, or fine and coarse glass fibres.

Asbestos was reported not to produce unscheduled DNA synthesis (UDS) in human fibroblasts. The tested asbestos concentrations in this experiment were probably low, since other effects (single or double strand breaks) were not found either (no other information available; Hart et al., 1979, cited by EPA, 1985). UDS was also not found in rat hepatocytes after treatment with 1-10 $\mu g/ml$ UICC chrysotile B (Denizeau et al., 1985). Treatment of hamster tracheal explant epithelium with 400 $\mu g/ml$ crocidolite did not increase the incorporation of [^{3}H]thymidine into the cells (Mossman et al., 1984). However,

fibrous erionite did cause increased unscheduled DNA synthesis in both mouse C3H,10T1/2 embryo fibroblasts and human A549 lung cells, at concentrations of 50-200 μg/ml (Poole et al., 1983). The same type of erionite also caused an increased morphological transformation in the former test system with erionite (see 2.4.5.). It is therefore interesting to note that this type of erionite, from Oregon, USA, caused almost 100% mesotheliomas of the pleura in rats after inhalation, whereas the mesothelioma incidence from similar asbestos concentrations was much lower -see 2.2.2.

UICC chrysotile and crocidolite did not cause DNA strand breakage in the alkaline elution assay when applied to cultured hamster tracheal cells (Mossman et al., 1983, cited by EPA, 1985), nor did UICC chrysotile, amosite and crocidolite in human broncial organ cultures (Lechner et al., 1983, cited by EPA, 1985).

In vivo human data

Rom et al. (1983) found a marginal increase in SCE levels in circulating lymphocytes with increasing years of asbestos exposure in a group of 25 asbestos insulation workers after controlling for age and smoking ($p = 0.056$). However, the slight increase in SCE rates in the exposed group compared with a group of 14 non-asbestos-exposed controls, was not significant. After controlling for age and asbestos exposure, the effect of smoking on SCE rates was highly significant for both groups ($p=0.002$). Only the rate of SCE in the longest chromosomes (group A) was significantly associated with both factors (asbestos exposure and smoking), with a significant statistical interaction between the two parameters. These results suggest that the SCE rates in asbestos insulation workers were slightly higher than in non- asbestos-exposed controls, but definite conclusions cannot be drawn because of the confounding effects of smoking.

Patients with asbestos-related malignant mesotheliomas were reported to excrete high levels of breakdown products of tRNA in urine. This is assumed to be caused by an increased turnover rate of tRNA in tumor tissue; it is also observed in some other types of cancer (Borek et al, 1977 and Sharma et al. 1983, cited by Solomon et al., 1985). By measuring these nucleosides in asbestos insulation workers without any clinical signs of malignancy, and in controls, 95% of the subjects could be correctly classified as positively or negatively asbestos- exposed; 10 out of 13 as having normal chest radiographs, and 27 out of 30 as exhibiting alterations in either the lung parenchyma or the pleura, or both (Solomon et al., 1985). This technique might therefore be

used as a new early screening method in persons at high risk of mesotheliomas.

2.4.5. Transformations

In vitro transformations were reported in SHE cells at concentrations of 2-4 $\mu g/cm^2$ for crocidolite, amosite and anthophyllite (DiPaolo et al., 1983), at 2 $\mu g/cm^2$ for chrysotile and crocidolite (Oshimura et al., 1984), and at unknown concentrations of crocidolite (Hesterberg and Barrett, 1984, 1985). Brown et al. (1983) did not find an increase in the number of transformed foci in C3H10T1/2 murine fibroblasts after exposure to 5 $\mu g/ml$ amosite or crocidolite. Fibrous erionite form Oregon, USA, caused increased morphological transformation in mouse C3H,10T1/2 embryo fibroblasts at concentrations > 10 $\mu g/ml$ (Poole et al., 1983).

2.4.6. Synergisitic effects

Simultaneous treatment of various strains of Salmonella typhimurium with asbestos and benzo(a)pyrene (BP) in the Ames test increased the mutation frequency compared to treatment with BP alone. The effect of combined asbestos/BP treatment was further enhanced by metabolic activiation. Treatment with asbestos only had no effect (Szyba and Lange, 1981). Treatment with both asbestos and BP also increased the mutation frequency at the HPRT-locus of adult rat liver epithelial cells, but the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) did not have any synergistic effect with asbestos (Reiss et al., 1983). Treatment with BP likewise increased morphologic transformation of SHE cells treated with asbestos, whereas UV irradiation did not (DiPaolo et al., 1983). Simultaneous treatment of rat hepatocytes with the mutagen 2-acetylaminofluorene (2-AAF) and UICC chrysotile B did not change the UDS response compared to treatment with 2-AAF alone (Denizeau et al., 1985). Treatment of hamster tracheal explant epithelium with either 400 $\mu g/ml$ crocidolite or < 2.5 $\mu g/ml$ (1 x/week) BP did not increase the incorporation of [^{3}H]thymidine into the cells; simultaneous treatment with both agents caused increased [^{3}H]thymidine uptake into the cells and development of squamous metaplasia (Mossman et al., 1984a).

2.4.7. Summary and conclusions

None of the commercial asbestos varieties had any mutagenic properties in bacterial systems (Chamberlain and Tarmy, 1977; Szyba and Lange, 1981); one natural asbestos variety seemed to be mutagenic in a reverse mutation test

with Escherichia coli CSH50 but this was probably due to contamination (Cleveland, 1984).

In in vitro mammalian systems, all tested asbestos varieties were able to induce chromosome aberrations, which consisted of numerical as well as structural changes, including exchanges (Hesterberg and Barrett, 1985; Huang et al., 1978; Lavappa et al., 1975; Oshimura et al., 1984; Price-Jones et al., 1980; Sincock and Seabrigth, 1975; Sincock, 1977, cited by EPA, 1985; Valerio et al., 1983). These mutagenic lesions may be a direct result of physical interaction of asbestos fibres with chromosomes and/or structural proteins of the spindle apparatus. The transformation of cells, which was also frequently reported after asbestos exposure in vitro, may be directly related to this mechanism (Hesterberg and Barrett, 1985). One report of weak mutagenicity of asbestos in CHO cells at the HPRT-locus (Huang et al., 1978; Huang, 1979) could not be confirmed by various other authors (Newman et al., 1980, cited by EPA, 1985; Oshimura et al., 1984; Reiss et al., 1982, 1983); the reported mutagenic action was probably secondary to cytotoxic damage. Testing of single and double DNA strand breakage in both human and animal organ cultures, and testing of unscheduled DNA synthesis in human fibroblasts (EPA, 1985) and rat liver hepatocytes (Denizeau et al., 1985), also gave negative results. In contrast, a type of erionite that was extremely potent in causing mesotheliomas in rats after inhalation, did cause increased UDS in both murine and human cell lines (Poole et al., 1983).

Only two in vivo mutagenicity studies have been reported, in mice and in monkeys; the results of single oral or intraperitoneal chrysotile administration were negative in both species (Lavappa et al., 1975). Although there is no conclusive evidence of an enhanced SCE rate caused by asbestos in in vitro animal systems (Livingston et al., 1985; Casey, 1983), data from occupationally exposed humans suggest that there is a weak relationship between asbestos exposure and SCE rate, which is greatly increased by cigarette smoking (Rom et al., 1983a). A striking increase in bacterial and in vitro mammalian mutagenicity was also observed after simultaneous treatment with asbestos and benzo(a)pyrene, but not with several other chemical mutagens or with UV irradiation (Szyba and Lange, 1981; Reiss et al., 1983; DiPaolo et al., 1983; Denizeau et al., 1985; Mossman et al., 1984a).

From the above data it can be concluded that, although asbestos does not cause gene mutations, it is able to cause chromosomal damage and in vitro transformation in cells into which asbestos fibres are able to penetrate. This effect is greatly enhanced by the presence of benzo(a)pyrene, and possibly

other polycyclic aromatic hydrocarbons, either in the medium surrounding the cells or adsorbed onto the fibres. Additional mutagenic mechanisms may be involved for the asbestiform mineral erionite, which caused unscheduled DNA synthesis in murine and human cell lines.

2.5. In vitro toxicity

2.5.1. Hemolysis

Various authors have reported that asbestos is hemolytic to blood from humans and various animal species in vitro, with chrysotile being much more potent than the amphiboles. Jaurand et al. (1983) reported a slower rate of hemolysis for amphiboles than for chrysotile, but a very similar final degree of hemolysis in vitro for all asbestos types and quartz. Because of its positively charged surface (due to Mg-ions), chrysotile very probably binds to the negatively charged sialic acid groups of the erythrocyte membrane, with consequent membrane deformations and cell damage. If Mg is leached from chrysotile, or if sialic groups are removed from the erythrocyte membrane, in vitro hemolysis of human blood is markedly reduced (Beck and Tilkes, 1980; Brody et al., 1983; Heppleston, 1984) although Jaurand et al. (1983) found that the rate rather than the extent of hemolysis decreased. Amphiboles have a negative surface charge, and are consequently more liable to bind to positively charged membrane components, like phospholipids and proteins (Brody et al., 1983). Leaching (=magnesium depletion) of amphiboles (see 1.3.1.) enhanced their hemolytic capacity (Light and Wei, 1977; cited by Yano et al., 1984). Fibre size is not expected to be important for this type of in vitro toxicity since it is caused by surface characteristics; in fact, extremely short-fibred chrysotile had a strong hemolytic activity (Pele and Calvert, 1983; Pele et al., 1983). The presence of dipalmitoyl phosphatidylcholin, a major constituent of lung surfactant, reduced the hemolytic capacity of amphiboles, and to a lesser extent, of chrysotile (Beck and Tilkes, 1980).

2.5.2. Cytotoxicity

Asbestos fibres have been reported to be toxic to a variety of mammalian cells in culture, including macrophages and macrophage-like cells, fibroblasts and epithelial cells of the lungs and trachea. Cytotoxicity appears to have two phases, as was described for macrophages (IPCS, 1986): a rapid phase, which is probably caused by direct interactions with the cell membrane as in hemolysis, and a more delayed phase, which may be caused by incomplete phagocytosis (see

2.5.3.) or by other mechanisms once the fibres have been taken up by the cells. Cytotoxicity is usually measured as the inability to form colonies (plating or cloning efficiency) or as increased membrane permeability (leakage of cytosolic enzymes like LDH; staining). An increased membrane permeability may also cause leakage of lysosomal enzymes and toxic cell metabolites (e.g. reactive oxygen intermediates) from the cells, which may be responsible for some pathological processes in vivo.

The cytotoxicity of fibres seems to be related to fibre size, with longer fibres generally being more toxic than shorter fibres of the same variety (Kaw et al., 1982; Beck and Tilkes, 1980; Chamberlain et al., 1982; Tilkes and Beck, 1982), although in one study exactly opposite results were reported (Yeager et al., 1983). Since most asbestos types differ in fibre size distribution, studies investigating differences in response for the various asbestos types are difficult to evaluate. Tilkes and Beck (1982) found no great differences between the toxicity of chrysotile, crocidolite, synthetic fluoramphiboles and glass fibres of similar geometric dimensions.

Normal human tracheobronchial epithelial cells were 10 to 15 times more sensitive to the cytotoxic effects of asbestos than bronchial fibroblasts from the same donor (Haugen et al., 1982).

2.5.3. Phagocytosis

Various cell types involved in in vivo phagocytosis of asbestos fibres have been studied in vitro. Macrophages, fibroblasts, mesothelial cells and epithelial cells of the lung, of different species, are able to incorporate asbestos fibres with a length of approximately < 5 μm and diameter < 3 μm; fibres with a larger diameter are not incorporated; longer fibres are often phagocytized incompletely, which causes local membrane damage with concurrent release of intracellular enzymes, and of toxic cell metabolites like reactive oxygen intermediates, as well as an increased cellular metabolism to compensate for the loss of enzymes (which means a permanent strain for the cells). Phagocytosis seems to be independent of the type of material (chrysotile, amphiboles, glass fibre; Beck and Tilkes, 1980).

Doll et al. (1982a,b) observed that human peripheral blood polymorphonuclear leukocytes had a reduced capacity to produce toxic reactive oxygen intermediates (which is a normal detoxification mechanism within macrophages), and a reduced capacity to phagocytize latex beads, after incubation with all asbestos types. According to the authors, this could not be ascribed completely to cell toxicity. Warheit et al. (1984a,b) found a similarly

decreased capacity for in vitro phagocytosis of rat pulmonary macrophages, both after shortterm inhalation of chrysotile in vivo and after incubation with crocidolite or wollastonite in vitro. Donaldson et al. (1985), however, found an increased production of reactive oxygen intermediates in mouse peritoneal macrophages after in vitro treatment with chrysotile. Although these results are not conclusive, they indicate that asbestos may be able to inhibit the normal phagocytic response of blood and lung macrophages to foreign particles.

2.5.4. Migration of macrophages and leukocytes

During normal phagocytosis, the macrophages release chemotactic factors that attract and stimulate other macrophages as well as leukocytes (Myrvik et al., 1985). Incubation of macrophages with various asbestos types resulted in a decreased release of those factors in vitro (Yano et al., 1984; Rola-Pleszczynski et al., 1984; Myrvik et al., 1985). This release-inhibiting effect was dose- related (Myrvik et al., 1985). Thus, high fibre concentrations may reduce the migration of phagocytizing cells towards inhaled fibres in vivo.

2.5.5. Immune response

A cellular immunoresponse (mitosis of immunocompetent cells, also called blastogenic response) can be induced by treatment of those cells in vitro with concanavalin A, phytohemagglutinin, pokeweed mitogen or other compounds. Intraperitoneal injection of mice with asbestos in vivo yielded peritoneal macrophages that were able to reduce the normal blastogenic response of mouse thymocytes to concanavalin A. However, treatment of mouse peritoneal macrophages with asbestos in vitro did not give them this reducing capacity (Donaldson et al., 1985). Therefore, a possible effect of asbestos on the cellular immunoresponse in vivo is probably mediated by macrophages that have been changed by asbestos via (a) factor(s) outside those macrophages.

In contrast, direct incubation of lymphocytes with asbestos did alter the blastogenic response of those cells to concanavalin A, phytohemagglutinin and pokeweed mitogen. Amphiboles decreased the blastogenic response of human blood mononuclear cells and T- cells; chrysotile did not give consistent results (Barbers et al., 1982; Bozelka et al., 1983a). Other fibres, like glass fibre and mineral wool fibre, were inactive.

These results suggest that asbestos may alter the immunoreactivity of organisms in vivo by direct interaction with lymphocytes, as well as by activation of macrophages by some unknown factor.

2.5.6. Summary and conclusions

Various authors have reported that asbestos is hemolytic to blood from humans and various animal species in vitro, which is an indication of interaction with cell membranes. Chrysotile is more potent than the amphiboles for this effect. Fibre size is not expected to be important here, since the effect is probably caused by surface characteristics (Beck and Tikes, 1980; Brody et al., 1983).

Cytotoxicity of asbestos fibres to a variety of mammalian cells in culture, as measured by the inability to form colonies or by an increased membrane permeability, is related to fibre size. Longer fibres are generally more toxic than shorter fibres (Beck and Tilkes, 1980; Tilkes and Beck; 1982; Chamberlain et al., 1982). The toxicity of asbestos fibres to phagocytizing cells may be caused by incomplete phagocytosis. The resulting increased membrane permeability, resulting in leakage of lysosomal enzymes and toxic cell metabolites from the cells, may be responsible for some of the pathological processes in vivo.

Asbestos fibres appear to reduce the phagocytizing capacity of macrophages in vitro (Doll et al., 1982a,b; Warheit et al., 1984a,b). The migration of phagocytizing cells towards inhaled fibres was also inhibited after exposure to asbestos in vitro (Yano et al., 1984; Rola-Pleszczynski et al., 1984; Myrvik et al., 1985). Thus, the normal clearance mechanism of the lungs for foreign particles may be reduced in vivo by asbestos exposure.

In vitro studies suggest that asbestos may alter the cellular immunoresponse of organisms, both by direct interaction with lymphocytes, and by activation of macrophages (Donaldson et al., 1985; Barbers et al., 1982; Bozelka et al., 1983a).

Although some effects observed in vitro may explain some of the processes in asbestos pathology, it must be stressed that they do not represent the situation in vivo and can only give an indication of the mechanisms involved.

3. EFFECTS ON MAN

3.1. Ingestion

Information about the effects on man of oral asbestos exposure is limited to the results of epidemiological studies that have been performed in areas with high asbestos concentrations in drinking water:

USA

-California -San Francisco Bay area (Kanarek et al., 1980; Conforti et al., 1981; Tarter, cited by Marsh, 1983; Conforti, 1983; Kanarek, 1983; Cooper, 1983)

-Connecticut (Harrington et al., 1978; Meigs, 1983)

-Florida -Escambia County (Millette et al., 1983)

-Minnesota -Duluth (Mason et al, cited by Marsh, 1983; Levy et al., 1976; Sigurdson et al., 1981; Sigurdson, 1983)

-Utah (Sadler et al., 1984)

-Washington -Puget Sound region, Seattle (Severson et al., cited by Marsh, 1983; Polissar et al., 1982; 1983; 1984)

Canada

-Quebec (Wigle et al., 1977)

-Other Canadian areas (Toft et al., 1981; Toft and Meek, 1983; Toft et al., 1984)

Some characteristics of these studies are summarized in table 12. All studies, except the case-control study of Polissar et al. (1983), correlated the incidence or mortality of GI cancer, and sometimes of other cancers, in the indicated geographic area with the estimated exposure to asbestos in drinking water. In most areas, subpopulations with high and low estimated exposure could be identified. Asbestos in drinking water originated from corroding asbestos-cement pipes in the distribution network (Connecticut, Florida, Utah), from contaminated surface water due to natural geological sources (California, Canada, Washington), or industrial/mining wastes (Canada, Minnesota). The studies have been critically reviewed by Marsh (1983), Erdreich (1983) and Toft et al. (1984). The main results, as outlined in those reviews, will be discussed below.

3.1.1. Geographical correlation studies

A general determination of the overall presence or absence of a positive association between the estimated asbestos exposure via drinking water and the

observed cancer mortality or incidence is presented in the tables 13 and 14. The data show that one or more studies have found, for males or females, some positive association for neoplasms of the pancreas(7x)[1], stomach (6x), bronchus/trachea/lungs (4x), esophagus (3x), peritoneum (3x), gall bladder (2x), pleura (2x), kidneys (2x), prostate (2x), small intestine (1x), colon (1x), rectum (1x), brain/central nervous system (1x), thyroid (1x); and leukemia/aleukemia (2x). However, there are many inconsistencies in these findings, even between studies in the same areas, accompanied by a considerable discrepancy in results for males and females, and there are many factors which may account for these inconsistencies.

Some factors are inherent to the study design. All studies except one were geographical correlation studies, which did not include any information on an individual level; location and average duration of residence and average water asbestos content of a certain geographical area were used for an estimation of exposure to asbestos, without corrections for migration, variability in daily water source, and confounding risk factors like occupational inhalatory exposure (Marsh, 1983; Erdreich, 1983). In the Californian studies of Kanarek and Conforti et al., somewhat more refined methods were used than in the other studies; for example, an attempt was made to correct, on a group level, for socio-economic variables. The Canadian studies of Wigle et al. (1977) and Toft et al. (1981) were seriously biased by occupational exposure: substantial proportions of the male labour force were employed in asbestos mining and milling (Toft et al., 1984) which is probably why positive associations were observed in males, but hardly in females. Occupational exposure may also have occurred in California and Connecticut (Marsh, 1983), but positive associations between asbestos ingestion and GI cancers were not limited to males in these areas.

Other factors, varying among the studies (see table 12) were:

-Duration of exposure and observation.

Since asbestos-related cancers have a long expected latency period (20-40 years), the Minnesota, Florida, Connecticut and Utah studies with a relatively short duration of exposure (see table 12) may give less positive associations at this early moment of observation, than at later stages (Erdreich, 1983). In Minnesota, regular updates of the earlier

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1) The number between parentheses indicates the number of studies in which a positive association was found.

investigations of Mason et al. (cited by Marsh, 1983) and Levy et al. (1976) have not (yet) shown significant trends for any effect with time (Sigurdson et al., 1981; Sigurdson, 1983).

-Exposure levels.

In California, where 4 subpopulations with different exposure levels could be identified, the trend of an increasing cancer incidence with increasing exposure level was highly significant in both males and females for combined digestive tract neoplasms and for combined digestive-related organ neoplasms, but not for neoplasms at single sites. The trend for respiratory cancers was highly significant in males only (which might be an indication of higher occupational exposure in residents of areas with high drinking water levels; Kanarek et al., 1980).

Exposure levels in Connecticut, Florida and possibly also Utah were low compared with the other areas (see table 12). Assuming a linear relationship between exposure and effects, the possibility of detecting any carcinogenic effects from asbestos ingestion is therefore lower in these studies than in the other studies, and negative results cannot be extrapolated to possibly higher exposure situations (Marsh, 1983b; Erdreich, 1983). However, since these relatively low exposure levels are probably representative for areas with asbestos cement pipes as the only source of fibers in drinking water, the results may reflect the absence of a risk for general populations in such areas.

-Detection potential.

Erdreich (1983) selected two studies (the California and Washington studies which were valid with respect to the above mentioned factors) to determine if they had the potential to detect the risk that was estimated by the EPA (1980) for asbestos ingestion (based on human inhalatory exposure data; this estimation has now been revised, because new animal ingestion studies have become available). It was concluded that these studies did not have the statistical power to detect such an expected risk. The positive associations found in these studies between asbestos ingestion and cancer of the stomach, esophagus and pancreas (California) and of the small intestine (Washington) can therefore only be considered qualitatively. Probability analysis for each cancer site, using the data from all studies represented in table 12, indicated that the stomach and the pancreas were the sites with the lowest probability of increased cancer by chance only (Marsh, 1983).

3.1.2. Case-control studies

A case-control study in Washington did not reveal any differences in oral asbestos exposure between a group of 382 cancer patients (cancer of the buccal cavity, pharynx, respiratory system, digestive system, bladder or kidneys) and a group of 462 unmatched controls. Asbestos exposure assessment was based on residence, workplace history, smoking and dietary habits, and individual water consumption data. Fitting of all data into a logistic regression model gave positive correlations between cancer at various sites and the major known risk factors (age, smoking habits); the only significant correlation between asbestos ingestion and cancer type was for stomach cancer in males. In females, however, this correlation was negative, which reduces the importance of this finding (Polissar et al., 1983; 1984). Other case-control studies have not been reported.

3.1.3. Summary and conclusions

Geographical correlation studies, relating a high asbestos level in drinking water to the cancer incidence or mortality in a certain region, generally suffered from bias from factors inherent to the type of study, as well as from severe other limitations (Marsh, 1983; Erdreich, 1983). Among the inherent factors was occupational exposure to asbestos (Wigle et al., 1977; Toft et al., 1981), which is probably why positive associations were observed in males but hardly in females in these studies. In many studies the average duration of exposure to asbestos at the moment of observation was shorter than the latency period for asbestos-related cancers (Marsh, 1983; Levy et al., 1976; Sigurdson et al., 1981; Sigurdson, 1983; Millette et al., 1983b; Harrington et al., 1978; Meigs, 1983; Sadler et al., 1984). In some studies the estimated exposure levels were low (Millette et al., 1983b; Harrington et al., 1978; Meigs, 1983; Sadler et al., 1984), which means that negative results cannot be extrapolated to possibly higher exposure situations. However, since these relatively low exposure levels are probably representative for areas with asbestos cement pipes as the only source of fibres in drinking water, the results may reflect the absence of a risk for general populations in such areas.

One series of studies potentially valid with respect to duration and level of exposure and population size (Kanarek et al., 1980; Conforti et al., 1981; Tarter, cited by Marsh, 1983; Conforti, 1983; Kanarek, 1983; Cooper, 1983) was highly suggestive of a positive association between asbestos ingestion and gastrointestinal cancer, with the stomach and pancreas being the least likely

sites to give cancer by chance only. However, these effects may have been the result of occupational or environmental exposure to asbestos, which could not be excluded in this region. Another potentially valid series of studies showed no positive association for these cancer sites (Severson et al., cited by Marsh, 1983; Polissar et al., 1982).
Only one case-control study has been reported; in this study cancer of the digestive tract and related organs did not show a consistent relation with asbestos exposure (Polissar et al., 1983; 1984).
Summarizing, it can be stated that the results of geographical correlation studies, relating asbestos ingestion to cancer incidence or mortality, are not reliable, although some are suggestive of a slightly increased risk of cancer of the stomach and pancreas. Since only one case-control study and no cohort studies are available, no firm conclusions can be drawn. Remarkably, adequate animal carcinogenicity studies are negative with respect to asbestos ingestion (see 2.2.1.).

3.2. Inhalation

Most information on the inhalatory effects of asbestos on man can be derived from occupationally exposed groups; some information is also available from environmental exposure. Detailed reviews of the most important available literature have recently been given by the EPA (1985), the IPCS (1986) and the WHO (1987). The main issues as outlined in these reviews will be discussed below.

3.2.1. Carcinogenic effects

There is sufficient evidence that asbestos is a human carcinogen after inhalation. All five major commercial varieties (chrysotile, crocidolite, amosite, anthophyllite and tremolite) have been linked to excess lung cancer and mesotheliomas of the pleura and peritoneum (EPA, 1985; IARC, 1982; IPCS, 1986; WHO, 1987).

Occupational exposure

The EPA (1985) reviewed 41 large and recent cohort studies of workers exposed occupationally to asbestos during manufacturing (gas masks; textiles; friction products; cement products), mining, or building/construction activities (insulation application; work at shipyards). The studies were listed according to the type of asbestos involved in exposure; however, the cohorts exposed to amosite and crocidolite had usually been exposed to chrysotile also, sometimes

in very considerable concentrations. Data are given in table 15. In the largest study (Selikoff et al., 1979), 922 cases of cancer as a cause of death were recorded among 17,800 insulation workers, against 320 expected, and cancer was thus increased from 19.3% to 43.8% of total mortality. The workers had been exposed to chrysotile and amosite (mixed exposure category). Because of its size, this study is probably the most appropriate to demonstrate the full spectrum of malignant disease from asbestos exposure. More specific data of this study are given in table 16.

Lung cancer (bronchial carcinoma)

As can be seen in table 16, lung cancer in the cohort of insulation workers examined by Selikoff et al. (1979) contributed most to cancer mortality (21% of total mortality). Upon review of all available clinical, surgical and autopsy material there appeared to have been some misdiagnoses: liver cancer secondary to lung cancer was often classified as the cause of death (Selikoff et al., 1979). Since lung cancer is a common form of cancer, similar misdiagnoses are expected in the general population, and a large effect on O/E ratios is therefore not probable.

Of the 41 studies reviewed by the EPA (1985), 30 showed an increased standard mortality rate (SMR) for lung cancer at the 5% level of significance, with SMR ranging from 1.25 to 8.75 (see table 15). The relatively large variability may be the result of different exposures in the different occupational groups, of different fibre types, and of a variety of other factors. All factors will be discussed using the data on exposure-response relationships that were established by the EPA (1985). Before exposure-response relations are discussed, some attention must be paid to the effects of age and of smoking.

-Time-age dependence.

Information on lung cancer risk from exposure at different ages is now available from two studies (Selikoff et al., 1979; Seidman, 1984) in insulation workers, first employed between 15 and 24 years of age, and 25-34 years of age, respectively. Plotting of the relative risk (O/E ratio) of lung cancer against age yielded identical curves with a distance of 10 years. This indicated that the relative risk is relatively independent of the age of first exposure. (The excess risk from asbestos exposure depends on the underlying risk, at zero exposure, which may be determined by many factors, among which cigarette smoking. This excess risk from asbestos exposure increases with age, with the greatest slope for first exposure at older ages; EPA, 1985).

If the data of the two studies are combined, there appears to be a linear increase in the relative risk of lung cancer with years from onset of exposure, with a latency period of approximately 10 years. After 40 years, there is a sudden decrease. The reason for this decrease is not understood; it may be partly related to termination of exposure, relatively earlier deaths of smokers, elimination of asbestos from the lungs, and individual differences in susceptibility. A decrease in relative risk after 35-40 years was also observed by other investigators (EPA, 1985).

-Smoking.

Hammond et al. (1979) investigated the influence of smoking on lung cancer in a large cohort of asbestos workers. During a period of 10 years, beginning 20 years or more after onset of exposure, 299 deaths from lung cancer occurred among 6841 smokers, and 8 among 1379 non-smokers, against 60.9 and 1.5 expected for non-asbestos-exposed smokers and non-smokers, respectively. (The expected data were based on standardized mortality rates in a control group of 73,763 white males exposed to dusts, fumes, gases or chemicals at non-farming work). Both the smoking and non-smoking lung cancer risk appeared to be multiplied approximately 5 times by asbestos exposure. However, smoking by itself caused an increase in lung cancer of approximately 10-11 times, and the risk of asbestos-exposed smokers thus was as much as 50-55 times higher than for non-asbestos-exposed non-smokers.

Other investigators reported similar results, although there was never as exact a multiplicative effect as in the former study. For example, an approximately 25 times increased risk in heavy smokers with high asbestos exposure was found compared to non-smokers with very low asbestos exposure in chrysotile mining (McDonald et al., 1980). The observed increase in mortality from smoking alone, however, was higher in the lower exposure group (11.8x versus 3.6x at high exposure) and the observed increase in mortality from asbestos-exposure alone was higher in non-smokers (6.9x versus 2.1x in smokers).

-Exposure-response relationships.

In 10 studies, lung cancer mortality data have been compared for several subgroups with different estimated cumulative asbestos exposure, thus providing exposure-response information. It must be stressed, however, that the estimation of longterm exposure from total particle count or mass concentrations to fibre concentrations, as measured at separate short-lasting occasions, is very inaccurate.

7 Studies showed a linear relationship between lung cancer mortality and estimated cumulative asbestos exposure (Dement et al., 1983a,b; McDonald et al., 1980; 1983a,b; Henderson and Enterline, 1979), in 2 the relationship was very weak (Seidman, 1984; Finkelstein, 1983) and in 1 the proportion of untraced individuals was too large to give reliable exposure-response information (Weill et al., 1977). However, although the relationship appeared to be linear, the slopes of the 7 given regression lines were different.

The EPA (1985) conducted a new regression analysis of all available studies providing exposure-response information (including the 10 mentioned studies and 4 others: Peto, 1980; Nicholson et al., 1978; Rúbino et al., 1977; Selikoff et al., 1979). It was found that a linear relationship between exposure and lung cancer response was likely in these studies. Estimates were made of the fractional increase in lung cancer risk per unit exposure (K_L, the slope of the regression line). Exposure was expressed as cumulative exposure in fibre- year/ml (f-y/ml). Data from all sources within each study were used; adjustments were made where necessary (for details see the EPA report). The results of this extensive analysis are illustrated in fig. 3, which shows the calculated values of K_L and its 95% confidence limits for the 14 studies. The calculated K_L varied roughly between 0.0001 and 0.07/(f-y/ml). In a similar analysis, Liddell and Hanley (1985) arrived at values for K_L ranging from 0.0004 to 0.015/(f-y/ml) (as cited by the WHO- report, 1987). In the WHO-report (1987), a value of 0.01 was adopted as a "best estimate" of K_L.

Although the existence of a linear relationship between exposure and lung cancer response is, in view of the inaccurate estimates of past exposures, not unanimously accepted, it seems to be the most likely and most practical assumption for a quantitative risk assessment (Doll, IARC, 1987).

-Different fibre types

Fig. 3 demonstrates that there is a large variability in K_L as calculated by the EPA (1985) and by Liddell and Hanley (1985), both within and between cohorts exposed to the same type of fibre. The variation may for a large part be due to to methodological limitations in exposure estimates and epidemiological assessment of the response, and to statistical uncertainties associated with a limited number of deaths. Furthermore, fibre size and exposure conditions may differ for various occupational groups (see below). For amosite and for mixed fibre exposure, the values for K_L were comparable to those for chrysotile in the textile production groups (EPA, 1985). Thus,

there is no evidence for differences in lung cancer response between the fibre types.

-Different occupations.

Chrysotile textile production imparts a significantly higher risk per unit fibre exposure than chrysotile mining and friction products manufacturing, although for the latter the uncertainties are greater. This is illustrated in fig. 3. These differences are probably caused by differences in fibre sizes involved in the different occupations: as the -initially long and curly fibred- chrysotile is processed, the percentage of respirable fibres increases (EPA, 1985; McDonald et al., 1984).

-Intermittent versus continuous exposure.

Short, intense exposures, as in some operations (e.g. insulation, maintenance) could have an effect different from longer and lower exposures to the same fibres. However, indirect information (no details; EPA, 1985) suggests that the magnitude of this effect, if present, is less than the variability between studies with continuous exposure. Henderson and Enterline (1979) found that the excess lung cancer risk for plant-wide maintenance mechanics was only slightly higher than that for production workers at the same plant, on a unit exposure basis; insulation workers exhibited similar unit exposure risks as groups with more continuous exposure (EPA, 1985).

Mesothelioma

The study of Selikoff et al. (1979) showed high mortality from pleural and peritoneal mesotheliomas in insulation workers exposed to both chrysotile and amosite. Certified were 25 cases of pleural, 24 cases of peritoneal, and 55 cases of unspecified mesotheliomas. Mesothelioma is a very rare type of tumor, probably causing less than 0.04% deaths in the general USA population (WHO, 1987), and therefore not easily recognized. Re-evaluation of the available information showed that many existing mesotheliomas had been misdiagnosed as pancreatic cancer, liver cancer or unspecified abdominal cancer. The numbers of cases after re-evaluation were 63 for pleural, and 112 for peritoneal mesotheliomas (2.8 and 4.9% of total mortality, respectively).

Pleural mesotheliomas and peritoneal mesotheliomas were found as a cause of death in 30 and 21 of the 41 studies reviewed by the EPA (1985), respectively. Expressed as % of total mortality, the values for pleural mesotheliomas ranged from 0.3 to 1.2% in chrysotile-exposed groups, from 0.3 to 3.1% in groups exposed predominatly to chrysotile, from 1.2 to 1.3% in amosite-exposed

groups, from 1.4 to 7.8% in crocidolite-exposed groups and from less than 0.1% to 8.3% in mixed exposure groups. For peritoneal mesotheliomas, these values ranged from less than 0.1 to 0.4% for chrysotile, from less than 0.1 to 2.4% for predominantly chrysotile, from 0.3 to 1.3% for amosite, from less than 0.1 to 11.3% for crocidolite and from less than 0.1 to 6.9% for mixed exposure. No mesotheliomas were reported in the only investigated group exposed to anthophyllite. However, misdiagnoses as reported by Selikoff et al. (1979) may have led to underestimations of this type of cancer in most studies.

-Time-age dependence.

In the studies of Selikoff et al. (1979) and Seidman (1984), the data on mortality from mesotheliomas in asbestos workers first exposed at ages 15-24 and 25-34, respectively, were roughly parallel, and separated by 10 years. Thus, the absolute risk of death from mesotheliomas appears to be independent of the age at which first exposure occurs (EPA, 1985). (The data for peritoneal and pleural mesotheliomas were combined in this analysis). This was confirmed by Peto et al. (1982) who reviewed the data from 5 cohort studies (Selikoff et al., 1979; Newhouse and Berry, 1979; Peto, 1980; Hobbs et al., 1980; Seidman et al., 1979) with respect to mesotheliomas.

Several authors reported that the relationship between mesothelioma death rates and time from first asbestos exposure was exponential rather than linear, with a delay of several years before the first cases appear:

$$I_M = c.(t-w)^k$$

with I_M = mesothelioma incidence (or death rate), c = an empirical constant (representing, or including, exposure), t = time since first exposure, w = the delay in expression of the risk (probably 10 years), and k = the empirically derived exponent. Peto et al. (1982) found that the data for 20-45 years from onset of exposure in 5 occupationally asbestos-exposed cohorts best fitted the expression using w = 0 and k = 3.2. Earlier mesothelioma death rates, however, were smaller than described by this equation; for all data up to 45 years from onset of exposure, w = 10 and k = 2 fitted better. Subjects exposed before 1922 and after 1946 and over the age of 80 were excluded; if these were included, a value of k = 5 was found to be more appropriate (EPA, 1985; Peto, 1980).

Plotting of the combined data of the studies of Selikoff et al. (1979) and Seidman (1984) showed that mesothelioma death rates in insulation workers

increased with time until 40 years from onset of exposure; at 50^{+} years from onset, a decrease could be observed as in lung cancer (EPA, 1985).

-Smoking.

No relationship was found between cigarette smoking and the risk of death from mesotheliomas (EPA, 1985; Hammond et al., 1979; IPCS, 1986).

-Exposure-response relationships.

From the 14 studies providing exposure-response information for lung cancer, only 4 were considered suitable by the EPA (1985) for a calculation of mesothelioma risk per unit exposure (Selikoff et al., 1979; Peto, 1980; Seidman, 1984; Finkelstein, 1983). For calculation of the mesothelioma risk per year, a linear relationship between unit exposure and risk was assumed, and the intensity and duration of estimated exposure were included in an integration of the mesothelioma/time equation (for further details see the EPA report). The estimates of mesothelioma risk thus obtained were relatively similar for 3 studies and higher for 1; however, there are too many uncertainties to draw conclusions. The ratio mesothelioma risk to excess lung cancer risk was remarkably constant, suggesting that the same factors involved in lung cancer also determine the incidence of mesotheliomas (EPA, 1985).

-Different fibre types

As in lung cancer, it is not possible to separate the effect of mineral type from other factors contributing to the variability found in mesothelioma death rates (EPA, 1985). However, most data are suggestive of a higher general mesothelioma risk after exposure to amphiboles, especially crocidolite, than to chrysotile (IPCS, 1986; IARC, 1987). Recent autopsy studies, in which the lung contents of mesothelioma patients working in different types of asbestos-processing industries were compared, appeared to confirm this. The lungs of chrysotile workers with mesothelioma contained up to 400x more (chrysotile) fibres than the fibres (amphibole) in the lungs of amphibole workers.

Peritoneal mesotheliomas have almost exclusively been associated with amphibole exposure (EPA, 1985).

-Intermittent versus continuous exposure.

Because of the exponential relationship of mesothelioma risk with time, longterm continuous exposure resulting in a certain cumulative fibre dose will very probably give a lower risk of mesotheliomas than exposure to the same cumulative dose in a short period of time. For shortterm exposure, the effects of continuous and intermittent exposure will probably be comparable.

However, there is no direct experimental evidence to support this (EPA, 1985).

GI_cancers

The study of Selikoff et al. (1979) showed a significantly increased mortality from cancer of the esophagus, stomach, and colon-rectum among asbestos insulation workers. Evaluation of 41 studies by the EPA (1985) demonstrated that the increase in GI cancer was usually smaller than that in lung cancer. Therefore, the studies giving no increase in lung cancer are probably not sensitive enough to detect any increase in GI cancer on a statistically significant scale.

In 10 out of 23 occupationally asbestos-exposed cohort studies powerful enough to detect increased GI cancer, an increased risk (expressed as O/E ratio) was demonstrated at the 5% level of significance. The relationship between increased GI cancer risk and increased lung cancer risk is very consistent (EPA, 1985). Because of the lack of confirming animal data and of a dose-response relationship, some authors ascribe the excess GI cancer mainly to misdiagnoses of lung cancer and mesotheliomas (EPA, 1985; IPCS, 1986). Although the EPA Cancer Asessment Group concludes that the evidence for a causal relationship between asbestos exposure and GI cancer is strong (EPA, 1985), the WHO considers the evidence for the induction of gastrointestinal cancers by asbestos weak and states that "the risk to the general population is very small, if any" (WHO, 1987).

A causal relationship between asbestos inhalation and GI cancer cannot be excluded. However, since the magnitude of the excess GI cancer after occupational asbestos exposure is considerably less than for lung cancer, the risk of GI cancer will not have a direct impact on the risk assessment with respect to asbestos inhalation in the general population. It must be stressed that the possible carcinogenic action of asbestos in the GI tract after inhalation does not imply that asbestos acts as a carcinogen after ingestion - see 5.

Other cancers

The study of Selikoff et al. (1979) showed a significantly increased mortality from cancer of the larynx, pharynx/buccal cavity and kidneys. Many other tumors were also increased, but not to a statistically significant degree for individual sites. As a group, all cancers other than those already mentioned were significantly increased (184 observed from best evidence versus 131.8

expected). Of the 41 studies reviewed by the EPA, 1 showed a significant increase in laryngial cancer, and 2 studies, both gas mask manufacturing with predominantly exposure to crocidolite, showed increased cancer of the ovary at a 5% level of significance. Although these data are suggestive, they do not give sufficient evidence of a causal relationship with asbestos exposure.

Non-occupational exposure

There are some indications that the risk of mesotheliomas may be increased for individuals who live near asbestos mines or factories. However, the proportion of recorded mesothelioma patients who live in the vicinity of asbestos mines or factories differs greatly for different areas, and little is usually known about the patients (e.g. about the duration of residence); the results of ecological studies (with asessment of exposure on population basis rather than on an individual level) are often biased by occupational exposure. There are no indications that the risk of lung cancer or other cancers may be increased from neighbourhood exposure. Furthermore, airborne fibre levels near asbestos facilities were generally much higher in the past than they are now (IPCS, 1986).

There are strong indications that household contacts (family, including pet dogs) of asbestos workers have an increased risk of mesotheliomas and lung cancer (Anderson et al., 1976; Glickman et al., 1983; IPCS, 1986). These data appear to be consolidated by the measurements of several times higher fibre concentrations in the homes of chrysotile miners compared with non-miners (Nicholson et al., 1980; IPCS, 1986). However, it must be noted that early day home fibre concentrations used to be higher than concentrations currently allowed in occupational situations; they can therefore not be considered to be low exposure situations.

Direct exposure-response information for very low exposure situations is not available. Mortality data from Canada, the USA, Norway, Finland and the United Kingdom suggest, however, that exposure to "background" levels asbestos (non-occupational exposure, as estimated from the effects in females) does not contribute much to the risk for mesothelioma and lung cancer. Since the start of the industrial application of asbestos in the 50's, when the mesothelioma incidence was low and identical for males and females, the mesothelioma incidence for males has risen steadily, whereas that for females hardly changed during the last 10 to 20 years (McDonald, IARC, 1987).

3.2.2. Noncarcinogenic effects

Asbestosis

Asbestosis is a chronic progressive fibrosis of the lung parenchyma (see 2.2.2.), which may cause shortness of breath and rales as the primary symptoms, and may in severe cases lead to weigth loss and ultimately to death. Asbestosis is characterized radiologically by small irregular opacities, usually on the lower and middle lung fields. In humans, this is often accompanied by evidence of pleural fibrosis or thickening (plaques), as well as pleural calcifications. It is mostly the parietal pleura that is involved, but the visceral pleura may also show lesions. Detection of asbestosis rarely occurs before 20 years from first exposure to asbestos under recent (=not exceptionally high) exposure conditions (IPCS, 1986; EPA, 1985).

Analysis of clinical and X-ray signs of asbestosis according to cumulative exposure in an asbestos textile factory suggested that the risk of developing asbestosis is less than 1 percent from an exposure to 0.7 f/ml for 40 years (= 28 f-y/ml; Berry et al., 1979). However, all individuals in this study were exposed for the first time to asbestos after 1950, and since asbestosis will progress after termination of exposure in the majority of cases, an increasing prevalence with time among this population cannot be excluded. Other analyses among populations of asbestos factories suggested a risk of radiographic abnormalities of less than 2 percent at cumulative exposures of 25 f-y/ml. However, findings of abnormal X-rays, predominantly of the pleura, among family contacts of asbestos workers suggest that very low exposures may produce signs of asbestosis if the time between exposure and observation is long enough (EPA, 1985).

The significance of minor X-ray changes is not clear. They may or may not be associated with decreased pulmonary function, and the association between X-ray changes and cancer risk is equally uncertain. Asbestosis as a cause of death, on the other hand, which is frequently noted among occupationally exposed cohorts (see table 15), was never reported in groups exposed to lower concentrations like family contacts (EPA, 1985).

Asbestosis mortality in heavily exposed workers seems to be related to time sinfirst exposure and to intensity of exposure (IPCS, 1986). However, it is very uncertain if the risk of the generalized progressive condition is linearly related to the intensity of exposure. Therefore, extrapolation of occupational exposure data to low exposure levels is not possible. The above observations indicate that asbestosis at low levels of exposure is not

expected to be an important problem; the primary risk consideration at those concentrations is cancer rather than non- malignant disease (EPA, 1985; IPCS, 1986).

3.2.3. Summary and conclusions

Carcinogenic effects

There is sufficient evidence that asbestos is a human carcinogen after inhalation. All five major commercial varieties (chrysotile, crocidolite, amosite, anthophyllite and tremolite) have been linked to excess lung cancer and mesotheliomas of the pleura and peritoneum (EPA, 1985; IARC, 1982). Of 41 occupationally asbestos-exposed cohort studies reviewed by the EPA (1985), 30 showed an increased standard mortality rate (SMR) for lung cancer at the 5% level of significance, with SMR ranging from 1.25 to 8.75. The relatively large variability may be the result of different exposures in the different occupational groups, of different fibre types, and of a variety of other factors. Mortality from pleural mesotheliomas occurred in 30 of the 41 studies (in 23 out of the 30 studies that were significantly positive for lung cancer). Mortality from peritoneal mesothelioma occurred in 21 of the 41 studies (in 19 out of the 30 studies that were significantly positive for lung cancer). However, many peritoneal mesotheliomas may have been misdiagnosed as pancreatic or other cancers (Selikoff et al., 1979). See also the table in this paragraph.

The relative lung cancer risk from asbestos exposure (observed/expected) appears to be independent of age. The excess risk (observed - expected) for mesothelioma (which is considered to be equal to the absolute risk, since the incidence in the general population is very low) is also independent of age. However, the excess risk for lung cancer linearly increases with age. The relative risk for lung cancer is approximately linearly increased with the time from onset of exposure, with a latency period of approximately 10 years, whereas the risk for mesotheliomas is rather exponentially increasing with the time from first exposure to asbestos. However, at 40-50 years after onset of exposure, there is a sudden decrease for both lung cancer and mesothelioma, which is only partly understood (Selikoff et al., 1979; Seidman, 1984; EPA, 1985).

Both lung cancer and mesothelioma risk are probably linearly related to the asbestos fibre concentration in air. In most cohort studies, however, fibre concentrations were not measured directly, but calculated from mass or total

particle count measurements. Therefore, the intensity of exposure to fibres, as given for these studies, can only be a rough estimate. Whereas some investigators feel that the existence of a linear relationship between fibre concentration and tumor incidence is only speculative, and that quantitative risk estimates based on these inaccurate data are not possible (IPCS, 1986; IARC, 1987), others nevertheless applied linear regression models to describe the relationship between the observed mortality from lung cancer in the various cohorts and the estimated cumulative exposure (Liddell and Hanley, 1985; EPA, 1985). During a recent IARC symposium it was reconfirmed that, despite all possible objections, a linear non-threshold extrapolation model seems to be the most appropriate model for a quantitative risk assessment of asbestos (Doll, IARC, 1987).

Mortality from mesotheliomas in 41 cohort studies (EPA, 1985).

Fibre type	Number of studies	Mortality[1], % of total mortality (n= number of studies with mesotheliomas > 0)	
		Pleural mesotheliomas	Peritoneal mesotheliomas
Chrysotile only	9	0.3-1.2% (4)	0.2-0.4% (2)
Predominantly chrysotile	6	0.3-3.1% (6)	0.5-2.4% (4)
Amosite	2	1.2-1.3% (2)	0.3-1.3% (2)
Predominantly crocidolite	5	1.4-7.8% (5)	0.9-11.3% (5)
Mixed asbestos	16	0.6-8.3% (12)	3.5-6.9% (8)
Anthophyllite	1	-	-
Talc (with tremolite)	2	-	0.9% (1)

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1) In populations without known asbestos exposure the mortality from mesotheliomas is very low (less than 0.04% of total mortality in the general population of the USA).

The effects of asbestos exposure and smoking appear to be approximately multiplicative. The number of deaths from lung cancer in a large cohort of asbestos workers, for example, was approximately five times higher than expected for both smokers and non-smokers; since smoking by itself caused approximately 10-fold increase in lung cancer mortality, the mortality from lung cancer in asbestos-exposed smokers was 50 times higher than in non-asbestos-exposed non-smokers (Hammond et al., 1979). No effect of smoking was observed for mesotheliomas.

There is no evidence for differences between the different asbestos types with respect to the lung cancer response (EPA, 1985). However, the data from cohort studies suggest that with respect to mesothelioma the amphiboles, especially crocidolite, are more potent than chrysotile (see the table in this paragraph). This appears to be confirmed by data from recent studies with lung autopsy material from mesothelioma patients. The lungs of mesothelioma patients who had been working in the chrysotile industry contained on average 400x more (chrysotile) fibres than the amount of (amphibole) fibres in the lungs of patients working previously in the amphibole-processing industry (Churg and Wright, IARC, 1987).

In 10 out of 23 occupationally asbestos-exposed cohort studies powerful enough to detect increased gastrointestinal cancer, an increased risk (expressed as O/E ratio) was demonstrated at the 5% level of significance. The relationship between increased gastrointestinal cancer risk and increased lung cancer risk is very consistent (EPA, 1985). Because of the lack of confirming animal data and of a dose- response relationship, some authors ascribe the excess gastrointestinal cancer mainly to misdiagnoses of lung cancer and mesotheliomas (EPA, 1985; IPCS, 1986). Although the EPA Cancer Assessment Group concludes that the evidence for a causal relationship between asbestos exposure and gastrointestinal cancer is strong (EPA, 1985), the WHO considers the evidence for the induction of gastrointestinal cancers by asbestos weak and states that "the risk to the general population is very small, if any" (WHO, 1987).

A causal relationship between asbestos inhalation and gastrointestinal cancer cannot be excluded. However, since the magnitude of the excess gastrointestinal cancer after occupational asbestos exposure is considerably less than for lung cancer, the risk of gastrointestinal cancer will not have a direct impact on the risk assessment with respect to asbestos inhalation in the general population. It must be stressed that the possible carcinogenic

action of asbestos in the gastrointestinal tract after inhalation does not imply that asbestos acts as a carcinogen after ingestion -see 5.

Other tumors were sometimes slightly increased in occupationally exposed cohorts but there is no evidence for a causal relationship with asbestos (EPA, 1985; IPCS, 1986).

There are strong indications that household contacts (family, including pet dogs) of asbestos workers have an increased risk of mesotheliomas and lung cancer (Anderson et al., 1976; Glickman et al., 1983; IPCS, 1986). These data appear to be consolidated by the measurements of several times higher fibre concentrations in the homes of chrysotile miners compared with non-miners (Nicholson et al., 1980; IPCS, 1986). The risk of mesotheliomas was also found to be increased for individuals who live near asbestos mines or factories (IPCS, 1986). However, it must be noted that early day home fibre concentrations used to be higher than concentrations currently allowed in occupational situations; they can therefore not be considered to be low exposure situations.

Direct exposure-response information for very low exposure situations is not available. Mortality data from Canada, the USA, Norway, Finland and the United Kingdom suggest, however, that exposure to "background" levels asbestos (non-occupational exposure, as estimated from the effects in females) does not contribute much to the risk for mesothelioma and lung cancer. Since the start of the industrial application of asbestos in the 50's, when the mesothelioma incidence was low and identical for males and females, the mesothelioma incidence for males has risen steadily, whereas that for females hardly changed during the last 10 to 20 years (McDonald, IARC, 1987).

Asbestosis

Analysis of clinical and X-ray signs of asbestosis according to cumulative exposure in an asbestos textile factory suggested that the risk of developing asbestosis is less than 1 percent from an exposure to 0.7 $f.ml^{-1}$ for 40 years (= 28 $f\text{-}y.ml^{-1}$; Berry et al., 1979). Other analyses among populations of asbestos factories suggested a risk of radiographic abnormalities of less than 2 percent at cumulative exposures of 25 $f\text{-}y.ml^{-1}$ (EPA, 1985).

The significance of minor X-ray changes is not clear. They may or may not be associated with decreased pulmonary function, and the association between X-ray changes and cancer risk is equally uncertain. Asbestosis as a cause of death, on the other hand, which is frequently noted among occupationally exposed cohorts, was never reported in groups exposed to lower concentrations

like family contacts (EPA, 1985). Asbestosis mortality in heavily exposed workers seems to be related to time since first exposure and to intensity of exposure (IPCS, 1986). However, it is very uncertain if the risk of the generalized progressive condition is linearly related to the intensity of exposure. Therefore, extrapolation of occupational exposure data to low exposure levels is not possible.

The above observations indicate that asbestosis at low levels of exposure is not expected to be an important problem; the primary risk consideration at those concentrations is cancer rather than non- malignant disease (EPA, 1985; IPCS, 1986).

4. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

4.1. Toxicity to aquatic organisms

Batterman and Cook (1981) determined chrysotile burdens in salmonids that had histories of asbestos exposure. Arctic char (Salvelinus alpinus) from Deception Bay, Canada, had 2.9 and 230.5 f/mg in muscle and kidney tissue, respectively, whereas the fiber concentration in water was 6.7×10^8 f/l (Batterman and Cook, 1981; cited in Belanger et al., 1986 and EPA, 1980).

Ecopathological studies on the effects of asbestos in aquatic organisms have not been performed in a systematic fashion. Black et al. (1982) described mesothelioma, a tumor type frequently associated with asbestos exposure in mammals, in walleye (Stizostedion vitreum) exposed to copper tailings that probably contained asbestos (Black et al., 1982; cited by Belanger et al., 1986). Other studies with asbestos in aquatic organisms have mostly been performed under laboratory conditions.

4.1.1. Algae

Cryptomonas erosa is a representative planktonic alga, commonly found in the Great Lakes area of the USA. Incubation of 5 ml Cryptomonas stock with 5 ml chrysotile asbestos solution (final concentration $1\text{-}1.5 \times 10^6$ f/l) for 72 hours resulted in the detection by TEM (transmission electron microscope) of asbestos fibers, especially smaller fibers, within Cryptomonas cells: in starch deposits, chloroplasts and ejectosomes. There was no evidence for phagocytosis or pinocytosis (Lauth and Schurr, 1984).

4.1.2. Molluscs

Halsband (1974) exposed mussels (Mytilus sp.) to high concentrations of chrysotile (1-100 mg/l) for 10 days, which resulted in accumulation of fibers in intestinal lining tissue. The fibers were not excreted when the mussels were subsequently placed in clean water (Halsband, 1974; cited in Belanger et al., 1986).

Asian clams (Corbicula sp.) were exposed to suspensions of chrysotile asbestos at 0, 10^4 and 10^8 f/l for 96 hours, with and without food, respectively. Siphoning activity (measured as the frequency of shell opening) was observed at 0, 0.5, 1, 2, 4, 8, 24, 48, 72 and 96 hours. The infiltration of asbestos fibers into gill tissue, visceral tissue and whole clam homogenate was examined by TEM after termination of exposure. Compared to untreated controls, the siphoning activity was significantly reduced within 8 hours in clams to

which no food was offered, at all asbestos concentrations alike; in clams to which food was offered, however, asbestos had no effect upon siphoning activity. Asbestos fibers were only found in whole clam homogenate of clams that had been offered food (69 f/mg dry tissue) at the highest asbestos concentration of 10^8 f/l (Belanger et al., 1986).

The experiments with Corbicula sp. where food was offered were extended to 30 days. Clams were observed once daily after feeding, and growth was determined by measuring shell growth and weight. At termination of exposure, visceral and gill tissues were examined by TEM. Siphoning activity was depressed in all asbestos-exposed groups alike, with a correspondingly decreased shell growth. Asbestos fibers were only found at the highest asbestos exposure of 10^8 f/l; 147 f/mg dry tissue was found in gills and 904 f/mg dry tissue in visceral tissue, with the average length of fibers in tissues being smaller than of those in water. Gill tissue appeared to be significantly altered after exposure to 10^8 f/l, with significantly more locules (fluid- filled open spaces between cells) in each lamella than for controls (Belanger et al., 1986).

During 14 days exposure to 10^2 to 10^8 f/l chrysotile asbestos, the larval release pattern of Corbicula sp. was studied. Exposure to asbestos seriously repressed the release of larvae in a dose-related way with no threshold level; larval mortalily increased with asbestos concentration (Belanger et al., 1986).

4.1.3. Fish

Belanger et al. (1985) exposed larvae of the coho salmon (Oncorhynchus kisutch) to 10^6 f/l chrysotile for 40 to 80 days. Lethargic behavior, epidermal hypertrophy, hyperplasia and selective vacuolation near the branchial region, and degradation of the lateral line system were noticed. Mortality was not observed (Belanger et al., 1985; cited in Belanger et al., 1986).

The Amazon molly (Poecilia formosa), a gynogenetically reproducing, live-bearing fish native to Texas, USA, was exposed for 6 months to several concentrations of coarse and fine chrysotile asbestos suspensions in a static test. (Coarse: all fiber sizes, concentrations 0.1, 1 and 10 mg/l; fine: mostly smaller fibers of 0.2-2 μm length, concentrations 0.01, 0.1 and 1.0 mg/l). (According to Cunningham and Pontefract (1973), 1 mg/l asbestos would be 10^{10} f/l; however, it must be stressed that this is only a very rough estimate since the mass:fiber ratio highly depends on fiber size). At the end

of this period, the fish were serially sectioned and the tissues examined for lesions. The kidneys were the major sites of accumulation of the fibers after their entry into the body through the intestinal mucosa. The accompanying table shows the numbers of fish with lesions of the gills and kidneys.

Numbers of surviving Amazon mollies showing lesions of the kidneys and gills after a 6-month exposure to various concentrations of chrysotile asbestos (Woodhead et al., 1983).

Asbestos (mg/l)	Kidney damage	Gill lesions
Coarse suspension		
0.1	4/17	8/17
1.0	5/15	13/15
10	4/14	13/14
Fine suspension		
0.01	0/20	0/20
0.1	12/20	2/20
1.0	17/17	5/17
Controls		
0	1/18	3/20

The number of animals with kidney lesions was greatest in the groups exposed to the finer particles, the probable reason for this being the preferential uptake of smaller fibers by the intestinal mucosa. Pathological changes in the kidneys were: selective necrosis of the hemopoietic tissue, fibrosis, and dilatation of tubules. The injury to the tissue may have resulted from the physical presence of fibers or from their chemical composition (magnesium). Small asbestos fibers would be expected to be easily taken up through the gills, and larger fibers to stay on the outer gill surface; this would explain the higher incidences of gill lesions that were observed in the groups exposed to coarse asbestos suspensions. However, there was no evidence of the entry of particles of any size through the gill epithelium. Nevertheless, epithelial hypertrophy and secondary lamellar telangiectasia of the gills, observed mainly in the groups exposed to coarse asbestos suspensions, appeared to be the result of external irritation of their surfaces by the asbestos particles.

There was no cellular injury in the liver or the muscles (Woodhead et al., 1983).

4.1.4. Summary

The impact of asbestos on aquatic life has largely been ignored. The few studies that are available -mainly laboratory studies- indicate that asbestos fibres are taken up by algae, molluscs and fish, and are able to cause morphological changes in those organs of fish that are involved in the uptake and concentration of fibres from water (gills, kidneys) at relatively high concentrations (10^8 $f.l^{-1}$; Laut and Schurr, 1984; Woodhead et al., 1983; EPA, 1980). In one study, asbestos was shown to affect the growth and reproduction of clams at lower concentrations, from 10^2 to $10^4 f.l^{-1}$ onwards (Belanger et al., 1986). The paucity of the data does not permit any conclusions about the possible effects of asbestos on environmental systems.

5. EVALUATION

The critical effect of asbestos for the general population is cancer.
The results of animal experiments with oral exposure to high concentrations of asbestos fibres are essentially negative. Results of human epidemiological studies relating asbestos exposure via drinking water to health effects are in some cases negative, in some cases there is a suggestion of an increased incidence of gastrointestinal tumors. However, there is a strong possibility of occupational or environmental exposure to asbestos in these studies which may well account for the positive correlations found.
Human occupational studies, in which exposure to asbestos has mainly been inhalatory, sometimes suggest an increased risk of gastrointestinal cancer. Although the evidence must be considered weak (animal inhalation studies did not confirm this risk, and some investigators attribute it to misdiagnoses of peritoneal cancers), a true causal relationship between gastrointestinal cancer and asbestos inhalation cannot be completely excluded. The possibility that asbestos may act as a gastrointestinal carcinogen after inhalation, however, does not necessarily imply a similar carcinogenic action after ingestion because of the differences in dimensions, concentration, and therefore of biokinetics and biological activity of the different fibres involved.
Because the evidence that asbestos may be carcinogenic by the oral route is very weak, the possible risk of cancer caused by ingested asbestos at the current exposure levels is considered neglectable. Therefore, a health based limit value for asbestos in food and drinking water is not proposed.

Inhalatory exposure to asbestos has been associated with cancer. Both from animal studies and human epidemiology there is adequate evidence that inhalation of asbestos may result in lung cancer and mesotheliomas. In some human occupational studies, an increased risk of gastrointestinal cancer was also indicated, but this was always considerably less pronounced than the risk of lung cancer. For a risk assessment, lung cancer and mesotheliomas may therefore be considered as the critical effects of asbestos inhalation.
The risks of lung cancer and mesothelioma have to be assessed separately because of the different exposure-response relations. Lung cancer is approximately linearly related to the duration and intensity of exposure, whereas mesothelioma appears to be related linearly to fibre concentration but exponentially to the time from onset of exposure.

The carcinogenic potency of asbestos appears to be a function of the fibre dimensions which may vary for the different types and brands of asbestos, depending on origin, application, type of processing etc. There is no evidence from inhalation and intrapleural/intraperitoneal animal experiments that chrysotile and the various amphiboles differ in carcinogenic potency as long as they have similar fibre dimensions and concentrations. On the other hand, mesotheliomas are less frequently noticed in epidemiological studies with mainly exposure to chrysotile asbestos, compared with studies in which the exposure was to amphiboles or mixed asbestos. The differences between animal and human data may partly be explained by the (slow) solubility of chrysotile in the tissues (whereas amphibole fibres accumulate in the perifery of the lungs and the pleura), which would account for a lower expression of the carcinogenic potency of chrysotile in humans compared to much shorter-living laboratory animals. However, it may not be possible to compare epidemiological data from different types of industry involving asbestos fibres of completely different dimensions. Fibre dimensions were not given in any of these studies. The results of recent autopsy studies are therefore important: these studies, with lung autopsy material from mesothelioma patients who had been working in different asbestos-producing and processing industries, confirmed that chrysotile may induce mesotheliomas, but in much larger fibre concentrations than the amphiboles. Doll and Peto (1985; IARC, 1987) suggested as a working hypothesis a 20x lower potency to induce mesotheliomas for chrysotile than for the amphiboles. With respect to the induction of lung cancer chrysotile and the amphiboles do not appear to differ.

A broad range of fibres can be inhaled, the upper limits of respirability being approximately 200 μm fibre length and 3 μm fibre diameter. Strictly spoken, "safe" fibre dimensions within the limits of respirability cannot be given, because carcinogenicity is considered to be a continuous function of fibre length and diameter. However, in practice the risk of fibres shorter than 5 μm will be neglectable.

Since no direct exposure-response information is available for very low exposure situations, the risk evaluation will be based on epidemiology from occupationally exposed humans.

Workplace fibre concentrations were usually not measured, but estimated from mass or total particle count measurements, with calibration methods using an optical microscope (OM) for which the detection limits are approximately 5 μm fibre length and 0.3 μm fibre diameter. The risk estimates in this evaluation will thus be based on optically visible fibres. However, fibres present in the

envionment generally have smaller diameters. Since fibres with a diameter of 0.1 to 0.2 μm are considered as the most critical, environmental fibre concentrations have to be measured by electron microscope (EM). To compare OM and EM concentrations a conversion factor has to be used; a factor 2 seems realistic for conversion of workplace to environmental situations (WHO, 1987; Cherrie, IARC, 1987).

The risk for lung cancer is approximately 10 times higher for smokers than for non-smokers, and is approximately multiplicative to the lung cancer risk from asbestos exposure. The risk for mesotheliomas is not influenced by smoking. Since so many uncertainties are involved in a quantitative risk assessment for asbestos, resulting in a broad range of possible risks, it is not considered scientifically appropriate to calculate a separate risk figure for non-smokers in the general population. The risk assessment as given in this document applies to the average general population with approximately 30% smokers.

A detailed description of the risk assessment in the WHO Air Quality Guidelines (1987) was given in a WHO working document (Appendix I of this chapter). The above mentioned risk assessment will be adopted in this Integrated Criteria Document, with modifications.

In the WHO Guidelines, an extra lung cancer risk was given in the range of 10^{-6} to 10^{-5}, and a mesothelioma risk was given in the range of 10^{-5} to 10^{-4} for lifetime exposure to 500 optically visible fibres per m^3, for all asbestos types, for an average population with 30% smokers. In this Integrated Criteria Document, an order of magnitude of 10-100 will be applied for the difference between chrysotile and amphibole asbestos with respect to mesotheliomas, and the ranges of risk given by the WHO Guidelines will be translated into ranges of fibre concentrations that can be associated with lifetime risks of 10^{-6} and 10^{-4}, respectively.

Risk assessment for the general population

Effect	Lifetime risk	Lifetime exposure: Optically measured fibres.m^{-3}	Lifetime exposure: Fibres.m^{-3} longer than 5 μm measured by EM[1].
Mesothelioma (for smokers and nonsmokers)	$1/10^6$	5-50 (amphiboles)	10-100
	$1/10^6$	50-5000 (chrysotile)	100-10,000
	$1/10^4$	500-5000 (amphiboles)	1000-10,000
	$1/10^4$	5000-500,000 (chrysotile)	10,000-1000,000
Lung cancer (population with 30% smokers)	$1/10^6$	50-500	100-1000
	$1/10^4$	5000-50,000	10,000-100,000

It must be stressed again that the figures as given in this table only give a rough approximation of the possible risks, but in general the assessment is believed to be conservative for the protection of health.

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1 Calculated with a conversion factor of 2.