IPCS/DHSS UK RISK ASSESSMENT SEMINAR LONDON 30 NOV - 11 DEC 1987

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SEMINAR, LONDON.
30 NOV – 11 DEC, 1987.

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18.12.87

30/11

Monday 30 Nov. 87 (1)

T. Hallmans.

Concepts of chemical Risk and Toxicology.

International Union Toxicology IUTOX.
Federation FEST.

Basic concepts

Risk at chemicals:

[The uncertainty of an unwanted effect] — when used chemicals.

Qualitatively: Damage of a living organism.
Quantitatively: The probability of that occurring.

1991

Factors of importance for risk at chemical.

1. Toxicity — the capability of a chemical to cause health damage in mas — qualitatively to the type, degree and extent and quantitatively related to the exposure, route, amount, time.
2. Exposure - Route
- amount
- time
→ Bioavailability
Biotransformation
Elimination.
3. The individual
- sex - dysfunction accumulation
- age - disease - external factors.
- genetic predisposition

Toxicity: damage on a living organism by chemicals — a property
— a capability
— an effect.

Risk = k × Toxicity × Exposure

↓ what will going to happen in the future.

Risk assessment: (Analysis std) → Risk quantification & risk evaluation.

~~probability directed to toxic~~

Risk assessment: — toxicity determination
— toxicity evaluation — extrapolate.
— hazard assessment —
— risk estimation — defined situation.
— risk evaluation — acceptable / not acceptable.

no event without risk.

Method of risk estimation:

Statistical projection
Extrapolation
- mathematical models
- safety factors
- expert statement

Method -
- intelligence - extrapolation
- information
- identification
- interaction
- initiation
- integration

⇒ ~~describe~~ describe into mathematical models

PAST	PRESENCE	FUTURE
Statistics	⟶	Risk
Damage in man →	Estimated toxicity ×	Exposure → Risk
Damage in an exp system →	Estimated toxicity in an experimental system. ↓ Evaluated toxicity in man ×	Exposure → Risk

How to express the risk of chemicals.
- Classification
- Unidimensional
- Two dimensional (numerically or verbally)
- Comparative, the toxic exposure Vs the aimed exposure
- Objectively, the toxicity facts.
- Relatively, in relation to other risks.

Problems:
Differences between animals and man.
Efficient concepts
No general rules
Lack of knowledge
Exposure assessment.

Recommendations:

Identify limits and possibilities
Accept the subjectivity
Support the awareness
Broaden the data-base
Phone research
Practice

11. 30pm (Cardiff) → 7.30am (Malaysia).

30 Nov.

W.R. Lee

Perception of Risk.

Language bring different meaning.

Occupation:	Fatal accidents / 10^8/yr
Clothing & Footwear	3
Textile	23
Chemical & allied features	87

1 in 10,000.

Difficult to give the value of ~~a car~~ ~~the~~ events.

- different people (of different interest) - give different value.
- to determine this value, we need various type of people with various interest.

How to make Risk = 0.

⇒ Impossible.

(Nobody can save their life) → but god.

- Risk. Man made & non.
- Living with Risk.
- Chemical risk.

Case Study I.

Evaluation of the carcinogenicity effect of lead chromate. 11.

1. Chemical-physical properties

Pure lead chromate is a gold to red powder with high specific gravity: 6.3 and very low solubility in water: 6x10-5 g/l.

2. Studies on the carcinogenic effect of lead chromate in man

2.1 Baetjer reported in 1950 8 lungcancer cases at 3 small factories producing lead and zink chromate (Ref No 5).

2.2 Langård and Norseth (Ref No 6) studied in 1975 a small factory in Norway producing chromate pigment among others lead chromate (but zink chromate and sodium dichromate was also produced). Among 24 male workers who had worked in the factory more than 3 years there were 3 workers with bronchial cancer and one with gastrointestinal cancer. This corresponds to a relative risk for lung cancer of 38 to be compared with the expected 0.079. The exposure was estimated to 0.5-1.5 mg/m3. A new study in 1983 at the same factory showed 6 deaths (0.135 expected) among the original 24 workers (Ref No 7). This corresponds to a relative risk of 44. Everyone except one worker who had got lung cancer had been exposed to zink chromate and only very sporadically to other chromates. Five of the six who had got lung cancer were smokers but the role of smoking in this population has not been studied.

2.3 Davies (**Ref No 8 and 9**) studied on two occasions (1979 and 1984) 3 factories in England where chromate pigment was produced, among others lead chromate. Davies found the following:

1979

Factory	Exposure	No of workers	Cases of lung cancer Observed	Expected
A	High and medium	175	18	8.17
	Low	77	2	2.00
B	High and medium	116	7	1.43
	Low	20	0	0.10
C	High and medium	96	1	2.46
	Low	19	1	0.37

1984

A	High and medium	333	21	9.45
	Low	260	7	6.95
B	High and medium	154	11	2.5
	Low	41	2	1.03
C	High, medium, low	241	7	6.45

In 2 of the factories (A and B) there was an increase in deaths due to lung cancer at high or medium but not at low exposure. In these 2 factories, besides lead chromate, zink chromate was produced. Zink chromate was not produced in the third factory (C).

2.4 Cooper (**Ref No 10 and 11**) studied on two occasions (1976 and 1983) 3 factories in the USA. He found the following:

Factory	No of workers		Cases with malignant tumors in the respiratory tract			
			Observed		Expected	
	1976	1983	1976	1983	1976	1983
1	247	246	2	3	1.1	2.3
2	166	164	0	2	0.6	
3	164	104	6	9	3.2	

Number of cases of lung cancer was on the first occasion too small to allow a statistical analysis. But the investigator concluded that there was a greater number of cases than expected in factory No 3. The follow-up showed no statistically significantly higher frequency of lung cancer than expected in factory 1, which only produced lead chromate. However the number of lung cancer cases taken together from factory 2 and 3 which except lead chromate even produced among others zink chromate was significantly higher than expected.

2.5 Frentzel-Beyme (**Ref No 12**) studied the lung cancer mortality in 5 pigment factories in Holland and West Germany. He found the fo llowing:

Factory	No of workers	Deaths in lung cancer	
		Observed	Expected
1	319	5	2.2
2	141	2	0.8
3	97	3	0.8
4	174	2	1.3
5	247	7	4.3

Even if the number of observed cases was higher at all factories the increase was statistically significant only at one factory, No 3. It is reported that all factories under the current time were producing both zink and lead chromate.

2.6 Sheffet et al (**Ref No 13**) studied a pigment factory in Newark. They found the following:

No of workers		Cases of lung cancer	
		Observed	Expected
Whites	Non-whites		
1296		21	16
	650	10	7

They concluded that there was a statistically significant relative risk of 1.6-1.9 for lung cancer among white workers and that there was also an increase among the non-white workers both of lung cancer and cancer of the stomach and pancreas. The factory produced both lead and zink chromate (proportions 9 to 1) but other chemicals, potentially carcinogenic, were also produced.

2.7 Conclusion

The reported investigations show that there are several cases of increased cancer mortality due to lung cancer among workers in factories producing different types of chromate compounds, among others lead chromate. However in none of these factories lead chromate seems to be the only product produced. On the other hand in all these cases other chromates, e g zink chromate has been produced which for several reasons (**Ref No 14**) has been considered a more probable cause of the increased cancer frequency than lead chromate.

Even if the epidemiological studies performed cannot exclude lead chromate as a cause of lung cancer in humans the present scientific view must be that there are no results showing that lead chromate causes cancer in man.

3. Studies on the carcinogenic effects of lead chromate in animals

There are several carcinogenicity studies performed in animals. In some cases the test material is only described as chromate dust. Whether it has contained lead chromate is not known. Below are only those studies presented in which it is clearly documented that the test material is lead chromate without the presence of any other chromate.

3.1 Steffee and Baetjer (**Ref No 15**) instilled lead chromate (0.3 ml of a 1% suspension) 6 times with 3 months' interval to 13 guinea-pigs. No lung tumors appeared during their life time. The same authors injected intratracheally 1 ml of a 1% suspension of lead chromate powder 3-5 times with 3 months' interval. No tumors were seen.

3.2 Furst et al (**Ref No 16**) injected 3 mg lead chromate in trioctanoin intramuscularly once a month during 4 months to 25 female mice. Two cases of lymphoma were seen within 16 months and 3 cases of a lungadenocarcinoma within 24 months among the 17 animals which were necrupsied. Similar frequencies of tumors were found both among control animals injected with the vehicle and among those not injected at all.

3.3 Maltoni (**Ref No 17**) found that a single subcutaneous injection of 30 mg lead chromate in water to 40 Spraque-Dawley rats gave rise to sarcoma on the injection site in 26 animals within 117-150 weeks. No case of sarcoma was found among the 80 control rats injected with the vehicle.

3.4 Furst et al (**Ref No 16**) injected 25 male rats and 25 female rats of Fischer-344-strain intramuscularly with 8 mg lead chromate suspended in trioctanoin once a month during 9 months. Lead chromate induced 14 cases of fibrosarcoma and 17 cases of rhabdomyosarcoma on the injection site in 31 of 47 rats. Furthermore 3 cases of kidney carcinoma among 24 lead chromate treated rats were found. The control group - 22 animals - injected with the vehicle did not show any such tumors.

3.5 Hueper and Payne (**Ref No 18**) implanted lead chromate intramuscularly. They found 1 tumor among 33 animals after 27 months. They also implanted lead chromate intrapleurally and found 3 cases of tumors among 34 animals after 27 months.

3.6 Levy (**Ref No 19**) implanted intrabronchially 2 mg lead chromate in 2 mg cholesterol with the help of a stainless steel net in 8 weeks old rats, 22 females and 48 males. The animals were sacrificed after 2 years. One case of bronchial cancer was found which was not statistically significant. No case of bronchial cancer was found among the controls. Six other qualities of lead chromate were tested in the same way. Three of them showed the same results as mentioned above, while no tumors were found for the other 3.

3.7 Conclusion

From the reported carcinogenicity studies in animals it can be seen that lead chromate causes sarcoma at the site of subcutaneous or intramuscular injections or intrapleural implantation. Furthermore 3 cases of kidney cancer were found among 24 rats given 8 mg lead chromate intramuscularly. On the other hand there were no statistically significant increase of lung tumors after 2 years of intrabronchial implantation of 7 different qualities of lead chromate. There is little doubt that the local sarcoma after injections are related to lead chromate while the relationship between lead chromate and the observed kidney tumors is doubtful. It is well known that different compounds with a very low solubility can produce this type of local tumors in rodents rather due to the unspecific physical properties as very low solubility rather than due to specific chemical properties as reactivity (Ref No 20). It has also been shown that these local sarcoma in rodents have no proven relevance to man (Ref No 21). Furthermore there was no significant increase in lung tumors after intrabronchial implantation which furthermore questions if the observed local sarcoma are indicative of any specific carcinogenic capability of lead chromate of importance to man.

4. Studies on other biological effects of importance for the evaluation of the carcinogenic properties of lead chromate

Different short term studies in particular of genotoxicity and mutagenicity could be of importance when evaluating the carcinogenicity of a chemical. Most of these short term studies are performed in vitro but due to the low solubility of lead chromate in water at physiological pH the possibility to study these effects are very limited.

4.1 Nestman et al (**Ref No 22**) have studied lead chromate dissolved with the help of sodium hydroxide or weak hydro chloric acid in different microbiel systems. They found that lead chromate dissolved in this way caused mutations in E. coli and S. typhimurium and mitosrecombination in Saccharomyces cerevisiciae.

4.2 Douglas et al (**Ref No 23**) examined chromosom aberrations and sisterchromatide exchange in cultured human lymphocytes and DNA-fragmentation in ovary cells from Chinese hamster. They found dose dependent chromosom aberrations and sister-chromatide exchange but no DNA-damage.

4.3 Petrilli and DeFlora (**Ref No 24**) found that lead chromate caused mutations in S. typhimurium.

4.4 Newbold et al (**Ref No 25**) studied the mutagenicity of among other things lead chromate in V79-cells from Chinese hamster. They found no effect of lead chromate and claimed that this was due to the low solubility of lead chromate.

4.5 Casto et al (**Ref No 26**) studied the effect of among other things lead chromate in a virus transformation system. They showed an increase in the virus induced transformation of primary hamster embryo cells which was of the same order of magnitude as that for more soluble chromate as potassium and zink chromate.

potential carcinogen

4.6 Conclusion

From the above investigations it can be concluded that chromates including lead chromate can cause genotoxic effects including mutations. It seems as these effects are correlated to the solubility of chromates in such a way that the higher the solubility the greater the effect, i e a suggestion of a direct dose-respons for the chromate ion. The fact that even lead chromate induces mutations

might be due to the solution of lead chromate with the help of acid or alkalie which has given a low but sufficiently high concentration of chromate ions. Whether similar chromate concentration can be obtained from lead chromate under physiological conditions is unclear. Thus lead chromate has a genotoxicity probably mediated via the chromate ion. It cannot be excluded that this can contribute to the possible carcinogenicity of lead chromate but there is no experimental support for this hypothesis.

5. Handling

Lead chromate is handled under different conditions, e g production, manufacturing of paints, at painting and at any work with products which have been painted with lead chromate containing paints. None of these types of handling exclude the possibility of exposure of personnel. Particularly at the latter situation it is difficult to estimate the size of the exposure while it ought to be rather low at painting.

CL

c) short term - exclusive.
d) Exposure levels not considered
c) levels not considered.
d) Exposure levels not defined

further action:
- Determine levels of both lead and zinc chromate and human if occurring
- Conveyorly animal studies after inhalation exposure
- Regulary monitor the workers.

Case Study 1

Public

Public includes :- Babies, children, Pregnant women, Elderly

Epidemiology studies only workers (15-65) old years.

Chromates are dangerous

If manufacturer says 'only Cr' is he sure it is true ?

cell tests → mutagenicity and

Animal studies are obsolete!

Is there a safety limit for carcinogen.

[even if low concentration carcinogens]

Manufacturer

According to the data lead chromate does not cause human lung cancer.

a) Exposure time too short.
b) Animal data (+ short term tests) inconclusive.
c) Smoking habits not considered.
d) Expose levels not defined

Further action:

- Determine levels of both lead and zinc chromate and human if necessary
- Conversely animal studies after inhalation exposure.
- Replace with the others.

Regulators:

Not adequate studies

1. Human studies
   - no adequate epidemiological data
   - level of exposure not specified.

2. Animal experiments not sufficient.
   - route of administration.

3. Warning & manufacturers.

a) nuzzle literature data.
b) epidemiological data
c) experimental data

Lead chromate is not carcinogenic pointer but hazardous test that 'T' class.

Zinc Chromate — carcinogen.
all chromate — "

(B) · The Public — receptor group · (all group) ·

Lead cromate is carcinogen ·

→ No laboratory experiment (study) ·

PHYSICAL DIFFERENCES

(Man – Rabbits)

MAN	RABBIT
COPIOUS AQUEOUS TEARS	SCANT VISCOUS OILY TEARS
EYELIDS TIGHT TO EYEBALL	LOOSE EYELIDS
NO THIRD LID	NICTITATING MEMBRANE
THICK CORNEAL MEMBRANE AND STROMA	MEMBRANES AND STROMA THIN
CORNEA HEALS QUICKLY	CORNEA SLOW TO HEAL

COMPARATIVE IRRITANCY REPORTED

RABBIT > MAN	RABBIT = MAN	RABBIT < MAN
SOME SOAPS	BENZALKONIUM CHLORIDE	NONIONIC SURFACTANTS
ANIONIC SURFACTANTS	TWEEN 80	TWEEN 20
DETERGENT FORMULATIONS (?)		
	PROPYLENE GLYCOL	ETHYLENE GLYCOL
	PHENOL	CRESOL
	STODDARD SOLVENT	
	KEROSENE	
	PETROLEUM OIL	
		ANTIHISTAMINE DRUGS
	OXALIC ACID	OZONE
	DIMERCAPROL	SELENIUM SULPHIDE
	PODOPHYLLUM POWDER	HAIRDRESSING FORMULATION

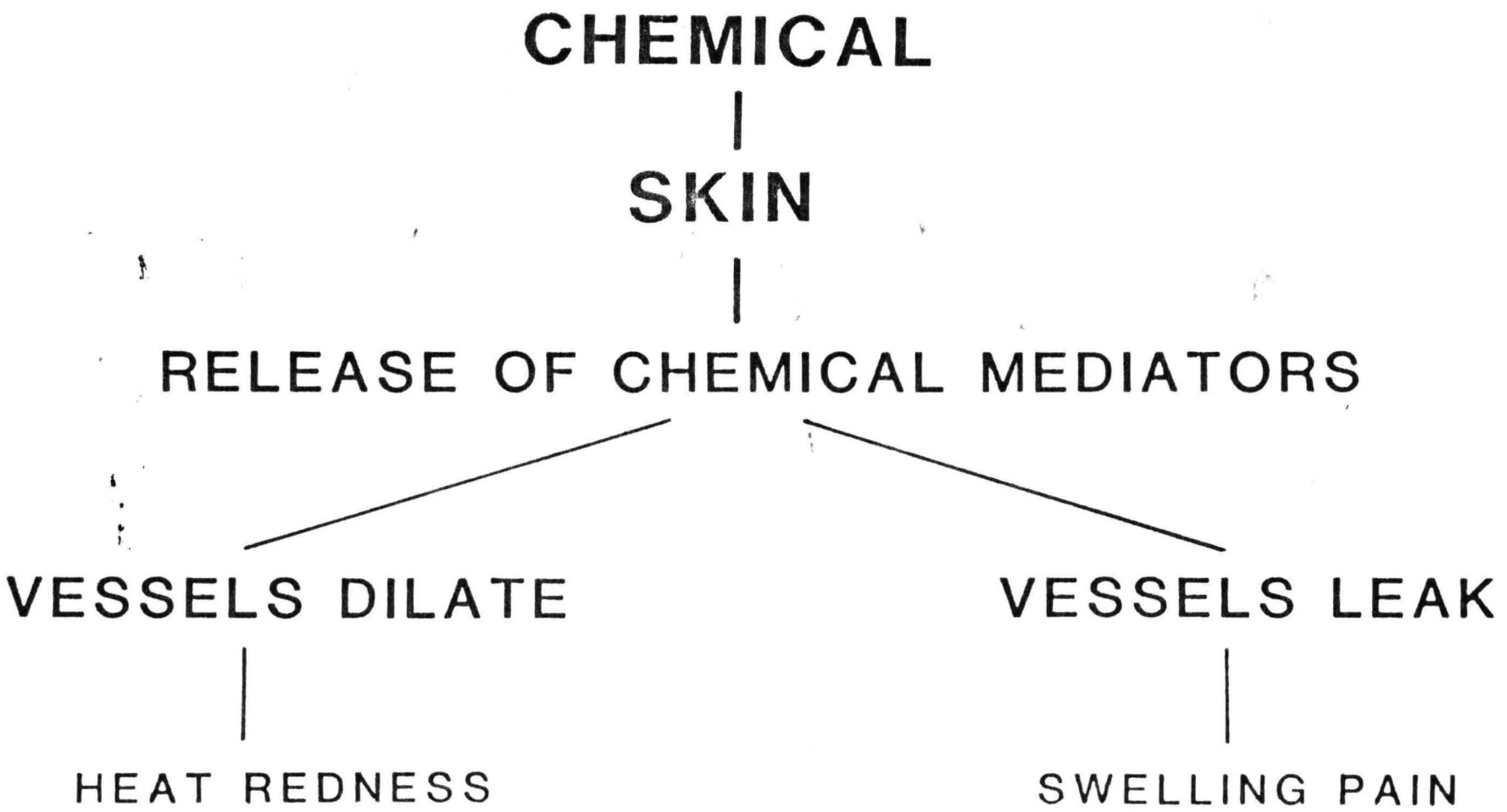
DERMATITIS

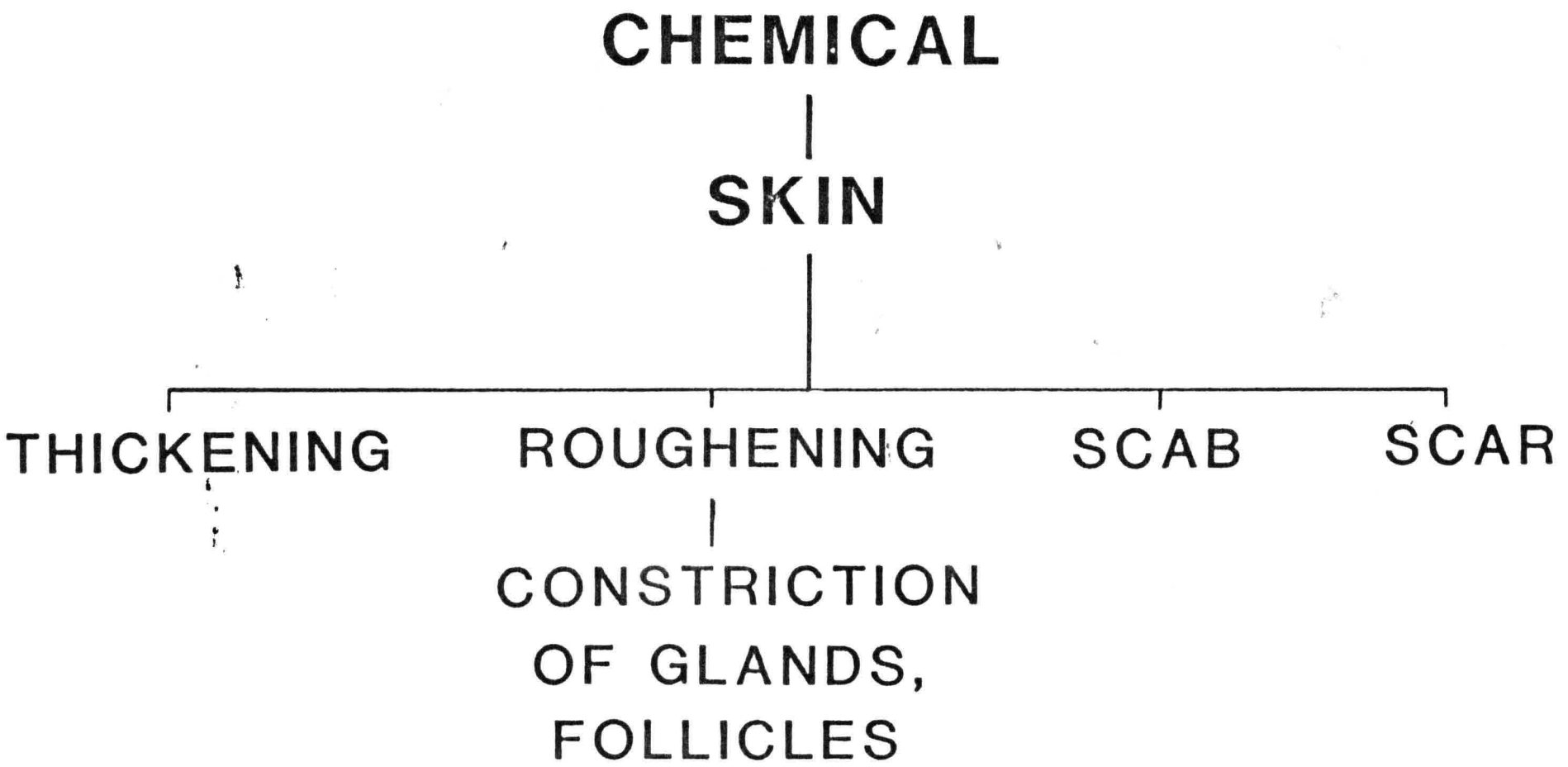
☆ MOST COMMON OCCUPATIONAL HEALTH PROBLEM

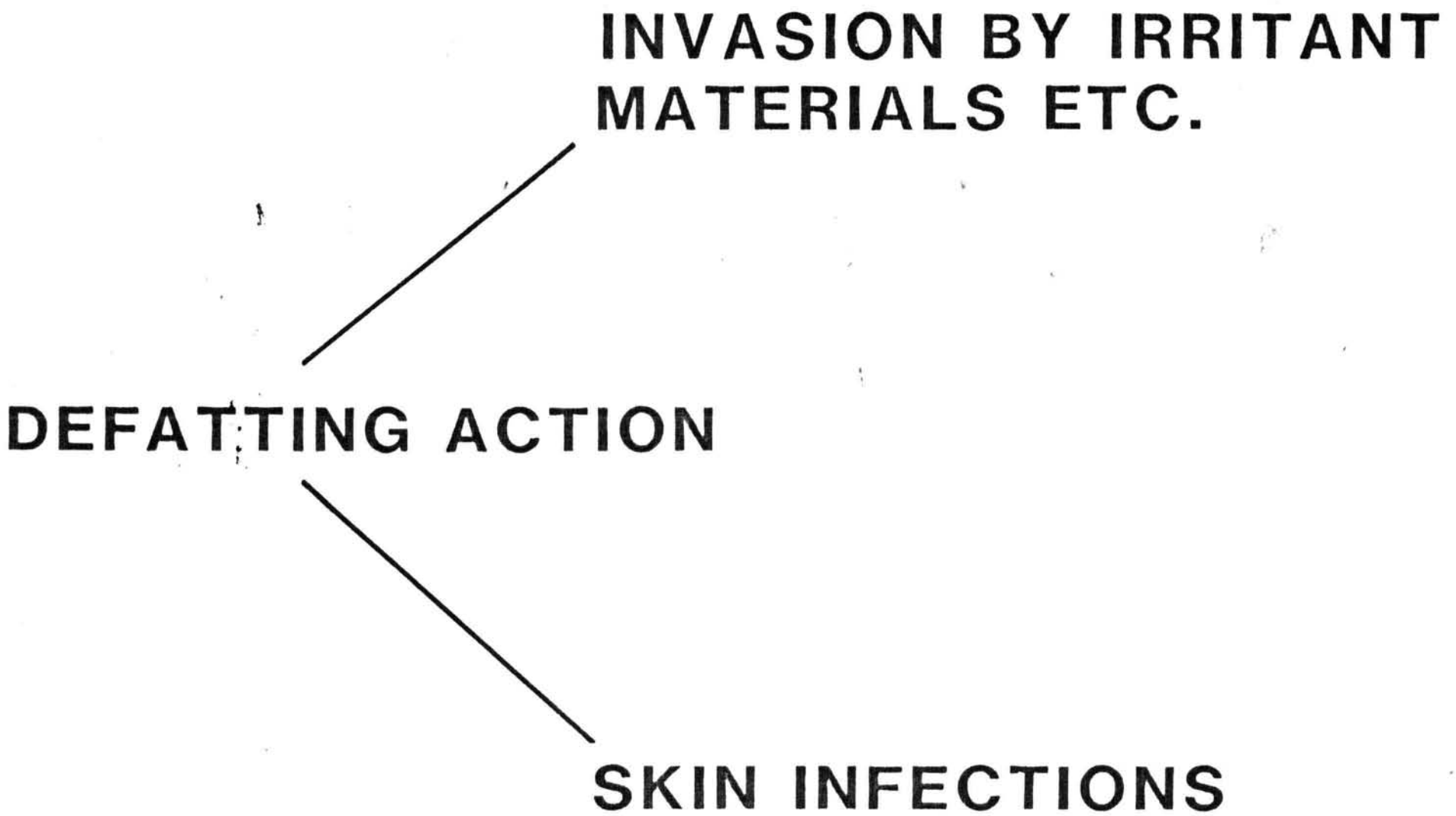
☆ 53% OF COMPENSATION CLAIMS IN 1986

☆ TIP OF ICEBERG

- LOCAL EFFECTS
  - -IRRITANT DERMATITIS
- EFFECT ON IMMUNE SYSTEM
  - -ALLERGIC DERMATITIS
- SPECIALISED EFFECTS
  - -SKIN TUMOURS
  - -CHLORACNE ETC.
- EFFECT ON ORGANS / TISSUES REMOTE FROM CONTACT


CHEMICAL
SKIN
RELEASE OF CHEMICAL MEDIATORS
VESSELS DILATE
VESSELS LEAK
HEAT REDNESS
SWELLING PAIN


CHEMICAL
SKIN
THICKENING
ROUGHENING
SCAB
SCAR
CONSTRICTION
OF GLANDS,
FOLLICLES


INVASION BY IRRITANT MATERIALS ETC.
DEFATTING ACTION
SKIN INFECTIONS

ALBINO RABBIT

ADVANTAGES

- WIDELY AVAILABLE
- EASILY HANDLED
- LARGE TEST AREA

DISADVANTAGES

- HAIRY
  - -INTERMITTENT GROWTH
  - -INCREASED SKIN VASCULARITY
  - -ENHANCED SENSITIVITY TO SKIN IRRITANTS
- EPIDERMIS
  - -THINNER THAN MAN
  - -NO SWEAT GLANDS
  - -MORE HAIR FOLLICLES

DRAIZE TEST

6 RABBITS

INTACT/ABRADED

SKIN 24-HOUR OCCLUDED PATCH

-ERYTHEMA/ESCHAR

NO ERYTHEMA	0
VERY SLIGHT	1
WELL-DEFINED	2
MODERATE-SEVERE	3
SEVERE/SLIGHT ESCHAR	4

-OEDEMA SIMILAR 0-4 SCORE

MODIFIED DRAIZE

4-HOUR

SEMI-OCCLUDED

3 ANIMALS

SAME SCORING SYSTEM

IRRITATION INDEX

USEFUL PREDICTOR

- -RELATIVE IRRITANCY
- -HIGHLY IRRITANT
- -NON IRRITANT
- -BRIEF/OCCASIONAL EXPOSURE

LABELLING PRESSURES FOR CLOSER CLASSIFICATION

BASED ON IRRITATION INDEX INAPPROPRIATE

POOR PREDICTOR

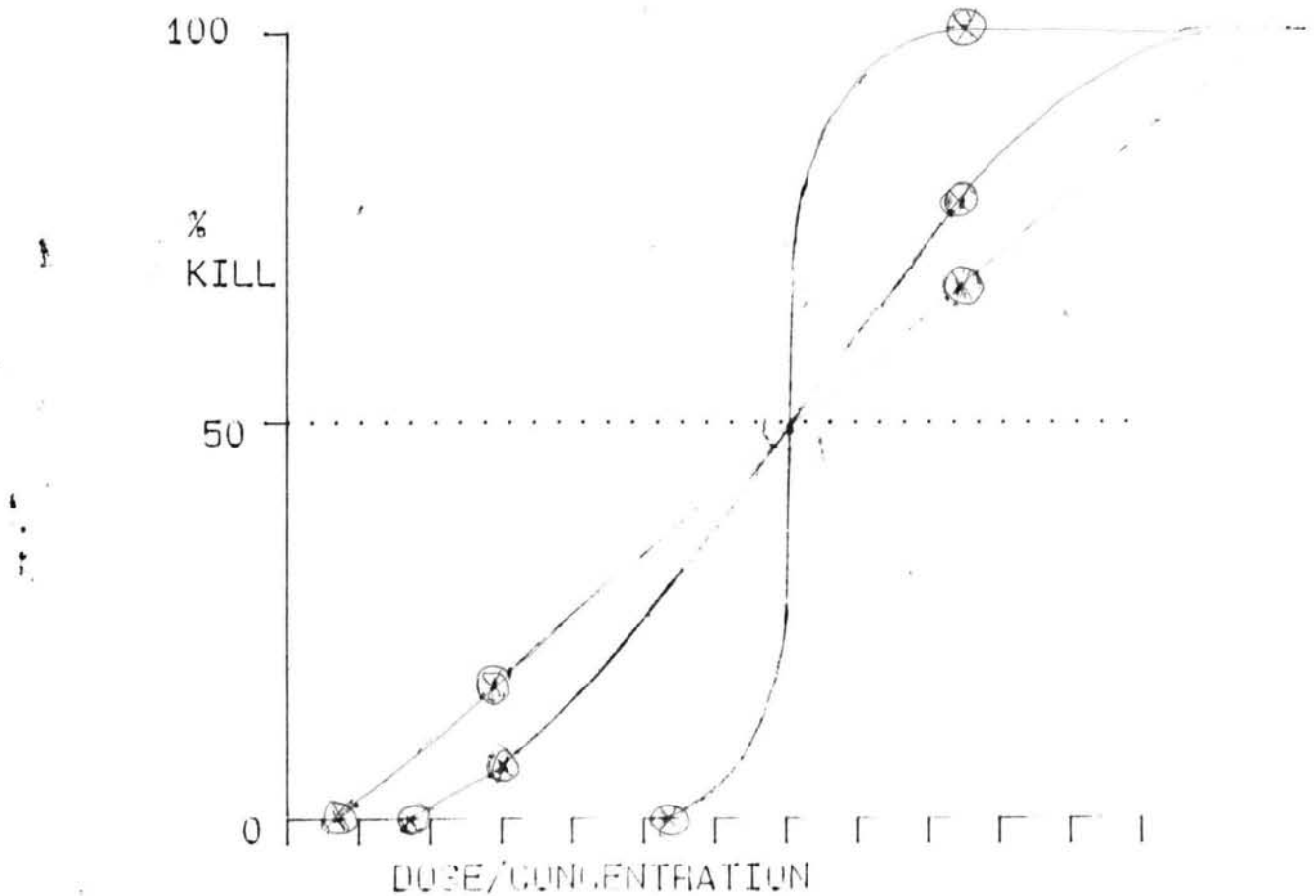
- -MODERATE IRRITANTS
  - INTER-LAB VARIABILITY
  - BIOLOGICAL VARIATION
  - **MISSING INFORMATION**
- -REPEAT/PROLONGED EXPOSURE

HUMAN EXPERIENCE MORE RELEVANT THAN ANIMAL DATA

CONCENTRATION ppm. FOR 1 HOUR

	Cl_2	HCN	C_2H_4O ethelene oxide	NH_3
NO THREAT TO LIFE (HIGHER LEVELS LETHAL)	25	50	2000	300
NO IRREVERSIBLE EFFECTS (HIGHER LEVELS - SERIOUS INJURY)	3	50	1700	100
HARMLESS OR EFFECTS JUST PERCEIVED	0.5	20	1500	25
	50/1	2.5/1	1.3/1	12/1

DETERMINATION OF LD_{50} / LC_{50}



ADMINISTRATOR/MANAGER NEEDS TO KNOW:

- LETHAL DOSE/CONCENTRATION, SUBLETHAL EFFECTS DOSE/CONCENTRATION, SEQUELAE

- SAFE ACUTE EXPOSURE CONCENTRATION

PHYSICIAN NEEDS TO KNOW:

- THE TOTAL RANGE OF ACUTE TOXIC EFFECTS, LIKELY SYMPTOMS OF OVEREXPOSURE, LONGER-TERM EFFECTS, MECHANISM OF TOXIC ACTION (TO DEVISE FIRST AID AND MEDICAL TREATMENT)

DETERMINATION OF ACUTE TOXICITY

INITIAL STUDIES

SUBSTANCE ADMINISTERED TO RODENTS
DOSAGE/EXPOSURE LEVELS FROM LETHAL TO HARMLESS
MOST RELEVENT ROUTES OF EXPOSURE

EXAMINE - GROWTH, FOOD CONSUMPTION, CLINICAL OBSERVATIONS,
BLOOD AND URINE INVESTIGATIONS, ORGAN FUNCTION TESTS,
PATHOLOGICAL/HISTOPATHOLOGICAL STUDIES AFTER FEW DAYS - WEEKS.

SUBSEQUENT STUDIES

SIMILAR STUDIES ON OTHER SPECIES

SIMILAR STUDIES USING OTHER RELEVANT ROUTES OF EXPOSURE

RATE AND DEGREE OF RECOVERY FROM TOXIC EFFECTS

EFFECTIVENESS OF POSSIBLE ANTIDOTES/TREATMENTS

MECHANISM OF TOXICITY. METABOLIC STUDIES

FOLLOW-UP OF WORKERS EXPOSED TO SUBSTANCE

"EYE IRRITATION"

CONJUNCTIVA	-	REDNESS SWELLING
DISCHARGE	-	SLIGHT, CLEAR COPIOUS, PURULENT
CORNEA	-	PITTING OF SURFACE OPACITY - REVERSIBLE - IRREVERSIBLE
IRIS	-	SWELLING
LENS	-	CATARACT
"HUMORS"	-	GLAUCOMA - INCREASE IN PRESSURE

METHOD:

1) PRE EVALUATION OF PHYSICO-CHEMICAL AND OTHER DATA E.G. pH 2-11.5

2) TOXICITY DATA - SKIN IRRITANCY
- EYE IRRITANCY OF SIMILAR COMPOUNDS

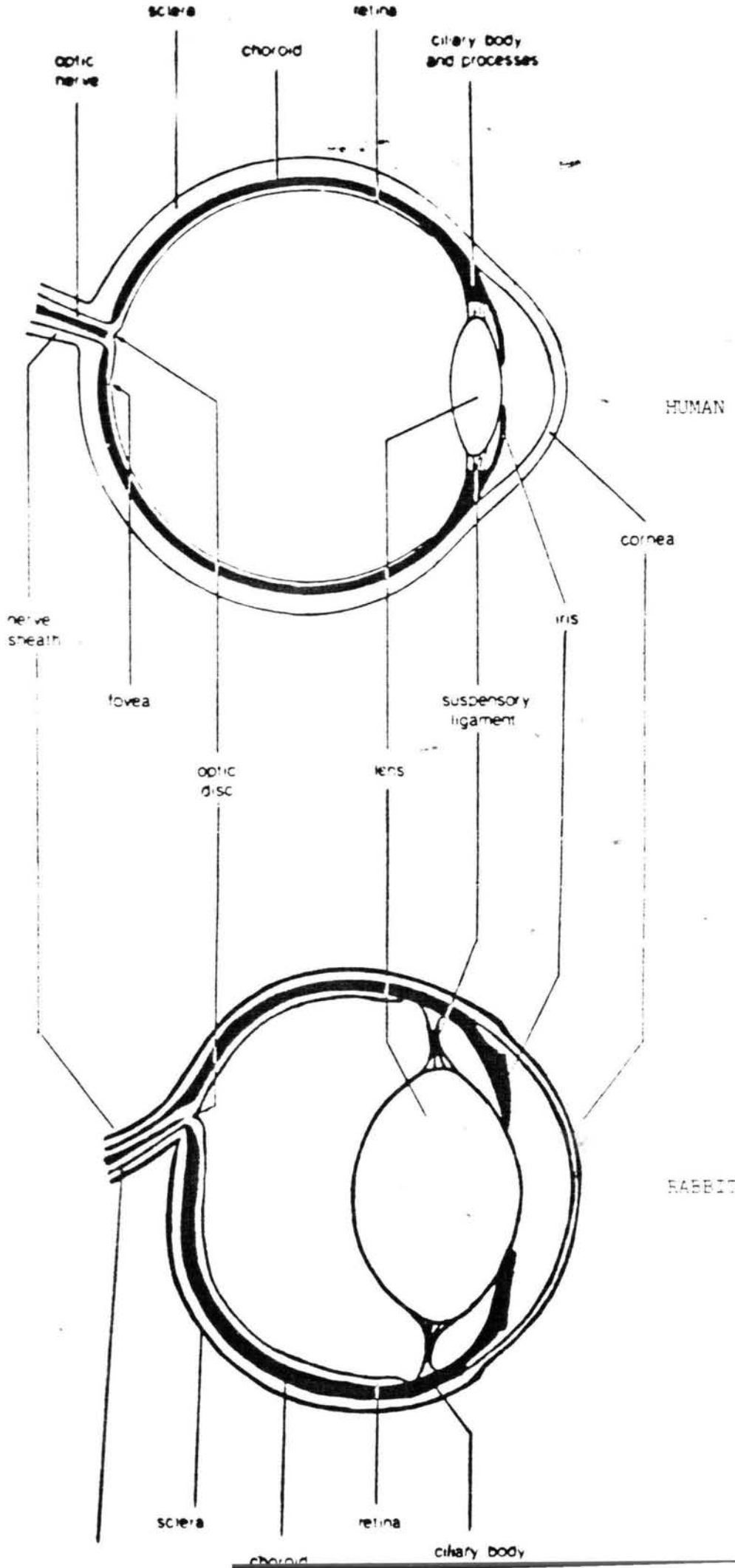
3) PRE-SCREEN IN A SINGLE ANIMAL

4) "DRAIZE TEST" - 0.1 ml OR EQUIVALENT WEIGHT
- EYES RINSED AFTER 1 - 10 SECONDS
- SCORE REACTION IN
CONJUNCTIVA
CORNEA
IRIS
OTHER

TABLE 1 Grades for Ocular Lesions

Description	Grade
Cornea	
Opacity: degree of density (area most dense taken for reading)	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	1[a]
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through opacity	4
Iris	
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperemia or injection, any of these or any combination thereof, iris still reacting to light (sluggish reaction is positive)	1[a]
No reaction to light, hemorrhage, gross destruction (any or all of these)	2
Conjunctivae	
Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Blood vessels normal	0
Some blood vessels definitely hyperemic (injected)	1
Diffuse, crimson color, individual vessels not easily discernible	2[a]
Diffuse beefy red	3
Chemosis: lids and or nictitating membranes	
No swelling	0
Any swelling above normal (includes nictitating membranes)	1
Obvious swelling with partial eversion of lids	2[a]
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

[a]Readings at these numerical values or greater indicate positive responses.


sclera
retina
optic nerve
choroid
ciliary body and processes
HUMAN
cornea
nerve sheath
iris
fovea
suspensory ligament
optic disc
lens
RABBIT
sclera
retina
ciliary body

TOXICITY/HAZARD/RISK

	DEFINITION	DEPENDS ON
TOXICITY	THE INNATE ABILITY OF A SUBSTANCE TO CAUSE INJURY - TOTAL OF ALL ADVERSE EFFECTS A SUBSTANCE CAN PRODUCE.	- THE SUBSTANCE.
TOXIC HAZARD	THE TOXIC EFFECTS RESULTING FROM A DEFINED EXPOSURE OR THE EXPOSURE LEADING TO DEFINED TOXIC EFFECTS	- THE TOXICITY - THE EXPOSURE - INDIVIDUAL SUSCEPTIBILITY
TOXIC RISK	THE PROBABILITY THAT MAN WILL BE INJURED BY A SUBSTANCE	- THE TOXIC HAZARD - THE PROBABILITY THAT MAN WILL BE EXPOSED

What is the risk of such materials.

ACUTE DISEASE	-	DISEASE WHICH COMES SHARPLY TO A CRISIS
ACUTE EXPOSURE	-	A SINGLE EXPOSURE OR MULTIPLE EXPOSURES DURING A 24 HOUR PERIOD
CHRONIC DISEASE	-	DISEASE WHICH SLOWLY DEVELOPS AND PERSISTS FOR A LONG PERIOD
CHRONIC EXPOSURE	-	CONSTANT OR REPEATED EXPOSURE OVER A LONG PERIOD (E.G. ONE TENTH OR MORE OF LIFE SPAN)
ACUTE TOXICITY	-	DISEASE WHICH DEVELOPS AND RESOLVES RAPIDLY FOLLOWING ACUTE EXPOSURE
CHRONIC TOXICITY	-	DISEASE WHICH DEVELOPS SLOWLY AND PERSISTS DURING OR FOLLOWING CHRONIC EXPOSURE

N.B. A) CHRONIC TOXIC EFFECTS CAN FOLLOW ACUTE EXPOSURE
B) DISEASE MAY APPEAR SUDDENLY DURING CHRONIC EXPOSURE

ACUTE TOXICITY

- EFFECTS ON TISSUES IN DIRECT CONTACT WITH THE SUBSTANCE, E.G. LIQUID HF, CL GAS.
- EFFECTS ON ORGANS AND TISSUES FOLLOWING ABSORPTION E.G. CAFFEINE, ORGANIC SOLVENT VAPOURS, NITROBENZENE.
- BOTH, E.G. PHENOL

ACUTE EXPOSURE (IN INDUSTRY)

- OCCURS VIA

MOUTH	- ORAL
RESPIRATORY TRACT	- INHALATION
SKIN	- PERCUTANEOUS
INJECTION	- S.C., I.D., I.M.

FOR EACH PRODUCT USED/PRODUCED, INDUSTRY SHOULD BE AWARE OF

- THE TOXIC EFFECTS OF ACUTE EXPOSURE, I.E. THE ACUTE TOXICITY
- THE TYPES AND DEGREES OF LIKELY EXPOSURE
- THE TOXIC EFFECTS OCCURING WITH SUCH EXPOSURES,
  I.E. THE ACUTE TOXIC HAZARDS
- THE PROBABILITY THAT THESE TOXIC HAZARDS WILL OCCUR,
  I.E. THE ACUTE TOXIC RISK

SO THAT PROCEDURES CAN BE DEVISED FOR

- SAFE HANDLING, USE, TRANSPORT AND DISPOSAL,
  INCLUDING SETTING ATMOSPHERIC LIMITS TO AVOID ACUTE TOXICITY
- FIRST AID AND MEDICAL TREATMENT OF OVER-EXPOSURE

HYDROGEN CYANIDE

SYMPTOMS DEVELOP IMMEDIATELY ON EXPOSURE -
HEADACHE NAUSEA, DIZZINESS, RR ↑ HR ↑ CONVULSIONS, DEATH

TOXICITY THE SAME BY ALL ROUTES) (ORAL, INHALATION, PERCUTANEOUS)

LETHAL DOSE 50-100 mg. SUBLETHAL EFFECTS RAPIDLY SUBSIDE WITH NO SEQUELAE. INACTIVATES ENZYME NEEDED BY TISSUES FOR UPTAKE OF OXYGEN. SPECIFIC ANTIDOTES AVAILABLE

METHANOL

SYMPTOMS DEVELOP 1-30 HOURS AFTER EXPOSURE - "ALCOHOL INTOXICATION" PLUS PARAESTHESIA, NUMBNESS, PAINS IN HANDS AND ARMS. VISUAL DISTURBANCES (LOSS OF ACUITY AND COLOUR PERCEPTION, SCOTOMAS, CONTRICTION OF FIELDS, EYE PAIN, PHOTOPHOBIA).

TOXICITY THE SAME BY ALL ROUTES (ORAL, INHALATION).

LETHAL DOSE 100ml. MANY SUBLETHAL EFFECTS REVERSIBLE; PERMANENT BLINDNESS, MILD DEMENTIA AND PARKINSONISM MAY REMAIN.

PRODUCES METABOLIC ACIDOSIS BUT TOXIC MECHANISM UNCERTAIN. SPECIFIC TREATMENT AVAILABLE.

20°C (hogarose.

METHYL BROMIDE

MILD EXPOSURE: NEUROLOGICAL SYMPTOMS DEVELOP IN A FEW HOURS - DAYS - GIDDINESS, ATAXIA, DIPLOPIA, PARAESTHESIAS EMOTIONAL DISTURBANCE, TREMORS, EPILEPTIC SIEZURES.

MODERATE EXPOSURE: STATUS EPILEPTICUS; LOSS OF CONSCIOUSNESS (IN CHILDREN - ENCEPHALOPATHY, HEPATOMEGALY).

HIGH EXPOSURE: HEADACHE, NAUSEA, VOMITING, BRONCHITIS, PNEUMONITIS, DELAYED PULMONARY OEDEMA, DEATH.

SKIN EXPOSURE: SUPERFICIAL BURNS.

TOXICITY DIFFERENT BY DIFFERENT ROUTES OF EXPOSURE.

LETHAL CONCENTRATION: 250-500 ppm

EARLY ~~ONLY~~ NEUROLOGICAL AND PULMONARY EFFECTS REVERSIBLE; HIGHER EXPOSURE LEADS TO PROLONGED NEUROLOGICAL AND PSYCHOLOGICAL DAMAGE.

MAY ATTACH TO -SH GROUPS IN BRAIN, ETC.; NO ANTIDOTE

LETHALITY IS ONLY ONE OF MANY TOXIC EFFECTS CAUSED BY EXPOSURE TO ANY SUBSTANCE.

TYPES OF SUBLETHAL EFFECT RANGE FROM TRIVIAL TO SEVERELY DEBILITATING.

MANY IMPORTANT TOXIC EFFECTS OCCUR AT EXPOSURES WELL BELOW THE LETHAL EXPOSURE.

SOME SUBLETHAL EXPOSURES CAN CAUSE PERMANENT INJURIES.

THERE ARE SPECIFIC ANTIDOTES AND TREATMENTS FOR ONLY A FEW ACUTE TOXINS.

Category	LD 50 absorbed orally in rats mg/kg	LD 50 absorbed percutaneously in rat or rabbit mg/kg	LC 50 absorbed by inhalation in rat mg/litre (4 hrs)
Very toxic	⩽ 25	⩽ 50	⩽ 0.5
Toxic	> 25 to 200	> 50 to 400	> 0.5 to 2
Harmful	> 200 to 2000	> 400 to 2000	> 2 to 20

If facts show that for the purposes of classification it is inadvisable to use the LD50 or LC50 values as a principal basis because the substance produces other effects, the substance shall be classified according to the magnitude of these effects.

Jan
FOOE (Anal)
1.12/87

DHSS/IPCS Risk Assessment Seminar

Acute Toxicity: Case Study I

Safe handling, use, transport and disposal of a substance and products which incorporate it.

Group A - develop scientific/medical advice required to ensure product safety and worker safety in relation to acute toxicity.

Group B - develop the manufacturer and marketer's view of how they can make and sell the product with minimum trouble to their business.

Group C - develop the view of a regulatory authority on the controls, product labelling etc. required to protect those manufacturing and using the substance and products containing it from any acute toxic hazards.

Substance - Ethylene glycol ($HO\ CH_2\ .\ CH_2\ OH$).

Uses - Chemical intermediate, antifreeze for motor vehicles, aeroplane deicing, hydraulic fluids, heat exchangers, solvent.

Physico-chemical Properties - clear, colourless, syrupy hydroscopic liquid with a sweet taste; Odourless; Mol. wt., 62.07; specific gravity, 1.11 at 20°C; melting point, 13°C; boiling point, 197.6°C; vapour pressure, 0.06 torr at 20°C; flash point, 115°C; saturation concentration in air at 20°c, 79 ppm; saturation concentration in air at 25°C, 131 ppm; miscible with water, alcohol and ether.

Biological properties

Acute Toxicity - Oral LD_{50}: Rat 5.89-13.4 g/kg bw: mouse 8.0-15.28 g/kg bw: rabbit 5 g/kg bw: Guinea pig 8.2-11.0 g/kg bw: dog >8.81 g/kg bw: lethal dose in man 1.56 g/kg bw.

Intraperitoneal LD_{50}: mouse 5.8 g/kg bw (no deaths at 0.58 g/kg bw).

Subcutaneous LD_{50}: mouse 10.0 g/kg bw (no deaths at 1.73 g/kg bw), rat 5.3 g/kg bw.

Acute effects in man

CNS effects (drunkenness, nausea, vomiting, depressed reflexes, nystagmus, coma, convulsions and death) seen $\frac{1}{2}$-12 hours after exposure.

Cardiopulmonary effects (tachypnea, tachycardia, hypotension, cyanosis, pulmonary oedema, cardiac enlargement, congestive heart failure, death) seen 24-72 hours after exposure.

Renal failure (oxaluria, increased NPN, anuria, acute tubular necrosis, death) seen following the above.

Eye irritation - single exposure of rabbit eye produced no appreciable irritation. One drop of 4% glycol in saline every 10 minutes for 6 hours caused conjunctival redness, mild conjunctival swelling and iritis;. a 0.4% solution had no adverse effects. Humans exposed to glycol spray (conc. 17 mg/m^3) showed no ill effect; a concentration of 265 mg/m^3 produced no damage in chimpanzees. Eye irritation, oedema of the eyelids and some corneal opacity were seen in rabbits and rats exposed to spray containing 12 mg/m^3.

Skin irritation - no signficant action on the skin. Skin becomes oedematous following severe and prolonged exposures.

Inhalation of Vapour - Rats were exposed to 500 ppm in air for 28 hr over 5 days. There was slight narcosis but no deaths. Rats and mice exposed to 140-160 ppm (350-400 mg/m^3) 8 hr/day for 16 weeks showed no injury.

Animals (? rats) exposed to vapour 24 hr/day for 3 months showed no effects at 0.3 mg/m^3 but depression of growth at 8.4 mg/m^3.

Rats, rabbits, guinea pigs, squirrel monkeys and dogs were exposed to 57 mg/m^3, 8 hr/day, 5 day/weeks for 6 weeks without adverse effects. Animals exposed for 24 hr/day for 90 days to 57 mg/m^3 showed moderate to severe eye irritation and corneal opacity (rabbits after 3 days, rats after 8 days).

Monkeys were exposed to 500-600 mg/m^3 glycol as aerosol for 2-3 weeks with no adverse effect. Even 5-7 months exposure produced no adverse effects in some animals.

Humans were exposed to glycol aerosol (particle size 1-5 μm) at a concentration of 3-67 mg/m^3 for 20-22 hr/day for 1 month. Some nasal and throat irritation, slight headache and backache were reported; 200 mg/m^3 was intolerable and 140 mg/m^3 very noticable.

Humans were exposed to 68.5 mg/m^3 of vapour + aerosol with no adverse effect. 137 mg/m^3 produced throat and eye irritation. 2055 mg/m^3 proved intolerable.

Long-term toxicity

The no-effect level (nel) of glycol in the diet of animals has been studied by several workers. Blood (1965) found this to be 100 mg/kg bw/day in a 2-year test in rats. Renal calcification and oxalate stones found at higher levels. Antonyuk (1974) found the nel to be 0.97 ml/kg/day in a 3-month study and Gaunt (1975) found that at and above about 180 mg/kg/day animals developed oxaluria and renal damage. Other studies have shown that monkeys could consume 0.14 - 0.17g/kg/day for 3 years without adverse effect, while 0.24 g/kg/day for 157 days caused oxalate deposition in kidneys.

Rats, rabbits. mice, guinea pigs, dogs and monkeys were exposed to 275 mg glycol/m^3 (100 ppm) for 3 weeks without adverse effect other than pulmonary irritation in rats and mice.

Absorption and metabolism About 60% of inhaled glycol vapour is retained by rats; much of it is deposited in the nasopharyngeal region. The half-life in rat blood was 53 hours. The predominant routes of elimination were in expired air (55-70%) and urine (14-26%).

Glycol is rapidly distributed into the body water. As much as 22% may be excreted unchanged in urine initially. Most is excreted as CO_2 by the lungs. Glycolic acid (HOOC.CHO) is also excreted in the urine (up to 30-40% of administered dose). The amount of oxalic acid formed varies in different species - 0.25 to 3.0% in laboratory animals, 2.3% in man and 18-20% in monkeys.

Mutagenicity - non-mutagenic in several systems.

Carcinogenicity - no tumours were caused by subcutaneous injection twice weekly for 1 year into rats which were maintained for a further 18 months. No tumours were caused by feeding a diet containing 1% glycol for 2 years to rats.

Teratogenicity - Groups of 20 pregnant rats were exposed to diets providing 1000, 200 or 40 mg/kg bw/day of glycol between the 6th and 15th days of pregnancy with no evidence of maternal toxicity and no significant foeto-toxicity or increased incidence of major malformations. Pregnant rats were administered glycol by gavage at doses of 1250, 2500 or 5000 mg/kg bw on each day from days 6-15 of gestation with no visible signs of maternal toxicity, although body weight was reduced. Foetuses from the middle and high-dose groups were lower in weight than controls and an increase was seen in the

incidence of malformation (1.4% in controls, 6.7% at 1250 mg/kg, 25.1% at 2500 mg/kg and 75.5% at 5000 mg/kg). The most common malformations were clefts in the lips, face and palate and skeletal abnormalities of the skull, ribs and vertebral column. A similar picture was found in pregnant mice administered 0.750, 1000 or 3000 mg/kg glycol, all dosage levels being affected.

In another study glycol was administered to pregnant rats and mice a daily dose of 2000 mg/kg/bw in drinking water and this induced a significant number of facial deformities in the young.

Mice and rats have also been exposed on days 6-15 of pregnancy (6 hours/day) to aerosols at concentrations of 0, 150, 1000 or 2500 mg glycol/m^3. This was without significant effect in rats but in mice on the two highest exposure levels there was an increase in the incidence of malformation of the head and skeleton. It is possible that some glycol was ingested as well as inhaled by these animals. The no-effect level was 150 mg/m^3.

Areas for consideration

1. What atmospheric concentration limits, if any, should be set for the workplace to ensure the absence of acute toxic reactions in the workforce? Is there a need to define a limit which should never be exceeded in the workplace? Is there need to set a limit which would ensure that workers are not exposed to excessive amounts during the whole working day (of, say, 8 hours)? If so, what should these limits be?

2. What other information, if any, would you require to set safe exposure concentrations for workers.

3. What other safety precautions should be advised to ensure worker safety while handling, using, transporting and disposing of the glycol? If personal protection is needed (e.g. gloves, respiratory protection), under what conditions would they be needed - continuously or for emergencies?

4. How should glycol be labelled to avoid acute toxicity if sold to the public in the pure form or in a concentrated form (e.g. as a car antifreeze)? Note women and children may be exposed as well as men.

5. Would there by any need to label a product of the following composition to avoid acute injury from glycol. The product is fictitious but might be a rust preventative paint.

Mineral oil, solvent refined	50%
Ethylene glycol	10%
Phosphoric acid	2%
Emulsifier	10%
Sodium nitrite	3%
Water	25%

DHSS/IPCS RISK ASSESSMENT SEMINAR

Acute Toxicity: Case Study 2

Measures required to protect workers and the local community from health risks associated with the accidental release of a dangerous substance stored on a factory site.

Group A - develop the view of commercial management responsible for running the storage site.

Group B - develop the scientific/medical advice required to eliminate or minimise hazards.

Group C - develop views of the local authority who wish the general public to be protected from accidental release of the substance.

Substance Ammonia (NH_3)

Scenario J. Bloggs & Co., wish to install two liquid ammonia storage tanks at their site which is situated near a village. See the map which shows the direction of the prevailing wind and the areas which mathematical modelling suggests will be enveloped for 30-60 minutes by the stated concentrations of ammonia gas following its release from the site following sudden massive rupture of the tanks (total storage capacity 25,000 kg).

Physicochemical properties Colourless gas at normal temperatures; strong irritating odour; mol. wt., 17.03; melting point, - 77.7°C; boiling point, - 33°C; vapour density, 0.59 at 25°C; soluble in water (90g/100 ml at 0°C); pH of 1% aqueous solution, 11.7; explosive limits, 16 to 25% by vol in air; odour threshold, 3.5 to 37 mg/m3 (5-53 ppm).

Biological Properties

Acute Toxicity - 50% of cats and rabbits exposed to 7000 mg/m^3 for 1 hour died with severe damage to upper respiratory tract, damage to bronchioles, alveolar congestion and oedema, atelectasis, haemorrhage, emphysema.

LC_{50} (2 hour exposure) of rats and mice is 7600 and 3310 mg/m^3 respectively.

Exposure to 35-70 mg/m^3 of ammonia for $2\frac{1}{2}$-3 hours decreased by 33% the respiratory rate of rabbits. Blood pH not affected but blood urea was raised by 25% and blood CO_2 by 32%. There were no adverse effects on the lungs, liver, spleen or kidneys.

Short-term toxicity

Guinea pigs, rats, rabbits, monkeys and dogs were exposed to 155 and 770 mg/m^3 ammonia for 8 hours a day, 5 days a week. No signs of toxicity, haematological changes or gross or microscopic pathological changes were seen at the lower concentration; higher concentration caused lacrymation in dogs and rabbits.

Continuous exposure of rats for 114 days to 4mg/m^3 produced no signs of toxicity. Rats exposed to 127 mg/m^3 for 90 days developed no abnormalities; rats exposed to 262 mg/m^3 for 90 days developed a mild nasal discharge; rats exposed to 455 mg/m^3 for 65 days showed mild dyspnoea and nasal irritation and 32/51 died by day 25 and 50/51 by day 65.

Following continuous exposure for 90 days to 470 mg/m^3 ammonia; 13/51 rats, 4/15 guinea pigs, 0/3 rabbits, 0/2 dogs and 0/3 monkeys died. Rabbits showed redness, discharge and corneal opacity in the eyes. Diffuse pneumonitis was seen in many animals.

Pigs exposed to 100 ppm for 2-6 weeks developed conjunctival irritation but no bronchial or alveolar injury.

Human Experience

Volunteers inhaled 21 and 35 mg/m^3 for 10 minutes; mild to moderate irritation was reported. 35 mg/m^3 for 5 minutes was not irritant to the eyes, nose, throat or chest but 94 mg/m^3 caused eye irritation, lacrymation, and nose and throat irritation in all volunteers and chest irritation in one person. Six subjects exposed to 17, 35 and 70 mg/m^3 for 2, 4 or 6 hours reported no discomfort but signs of nasal irritation were seen. All 7 volunteers reported severe respiratory tract irritation when exposed "nose only" for 30 minutes to 35 mg/m^3. 16 volunteers were exposed to 50, 80, 110 and 140 ppm ammonia for 2 hours with no effect on ventilatory capacity or 1-sec forced expiratory or respiratory volumes. Eight of them found 140 ppm so severely irritant that they terminated exposure before 2 hours.

Strong ammonia solutions in water produce severe eye and skin injury following short periods of contact. Very high concentrations of vapour have been shown to produce chemical burns, blisters and severe oedema of the eyes, nose and throat with coughing, dyspnea and progressive cyanosis. Shock and chemical pneumonitis occur in severe cases with death from pulmonary oedema.

Residual effects following exposure include decreased respiratory function and bronchiectasis.

Areas for consideration

1. What gas concentrations are likely to produce

   a) minor adverse effects which are not life threatening?
   b) more severe adverse effects which may require medical treatment to avoid fatalities or residual injuries?
   c) death?

   Note in considering this, exposures for $\frac{1}{2}$-1 hour might be expected.

2. Are there enough toxicological and human data to judge the risks?

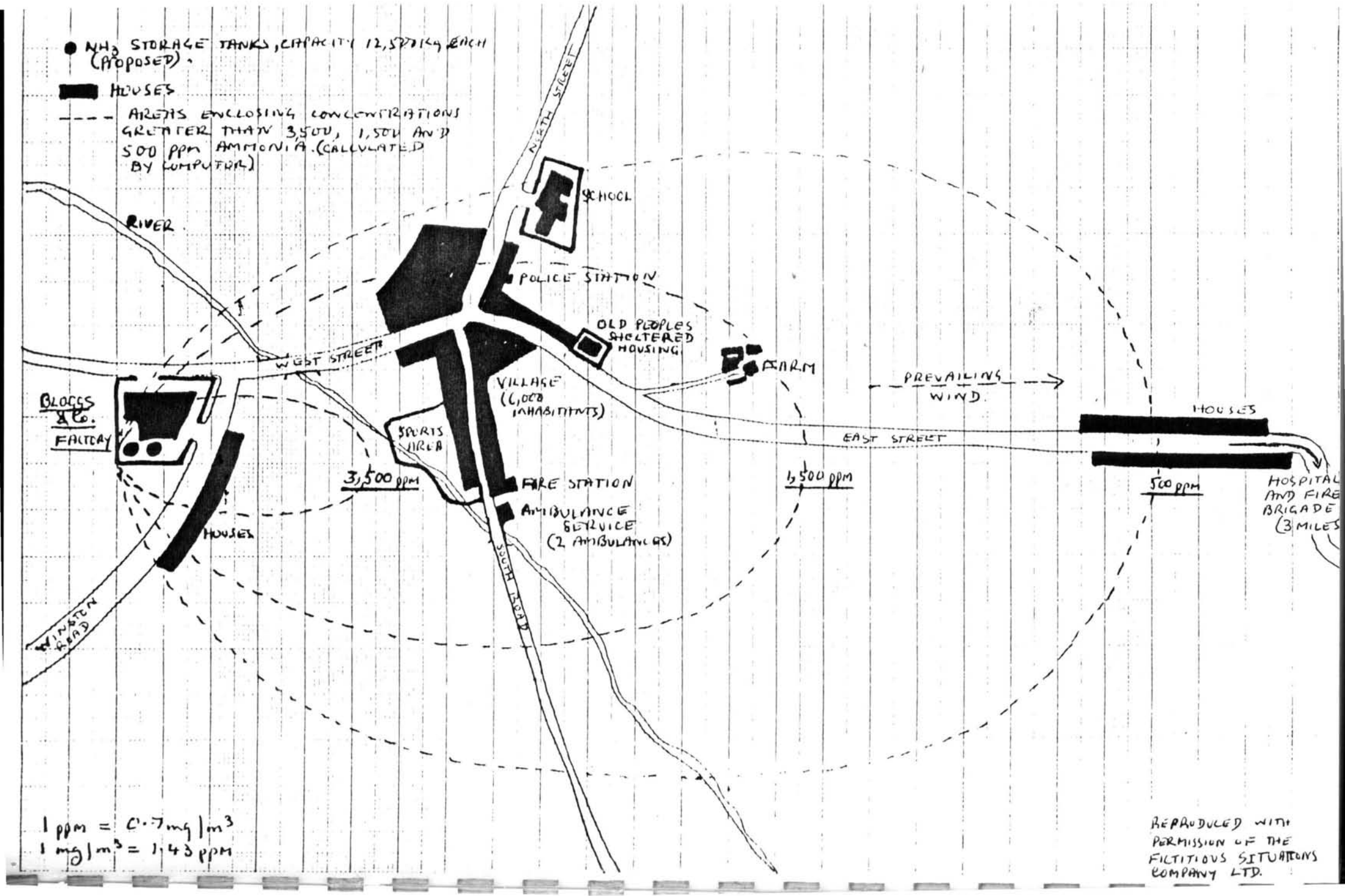
3. How accurate are the forecasts produced by mathematical modelling of exposures likely to be?

4. What is the likelyhood of a massive ammonia release occurring and is any extensive emergency planning actually necessary?

5. What emergency plans might be developed by the authorities (police, hospital, ambulance service, emergency rescue and fire service) in conjunction with Bloggs and Co?

6. Should the storage of 25,000 kg of ammonia be allowed on the site (if ammonia storage is not allowed Bloggs and Co. will move their factory with the loss of 500 jobs in the village)?

7. If storage of 25,000 kg of ammonia is allowed what could be done to make a safer situation?



1 ppm = 2.5 mg/m³

Case Study 1

A: Scientist -

Ethylene Glycol.

Recommended workplace

Level – 50ppm

T_{LV} – 5ppm.

Safety Precautions: –

1. No women employed of child-bearing age.
2. Face-masks to be worn in emergencies.
3. Regular monitoring of urine
   - kidney function.
   - ~~Oxygen~~. Oxaluria.
4. Ban in the work areas of;
   - Food.
   - Drink.
   - Smoking

(5). Labelling – hazardous to health NOT for internal use.

B: Industry:

Level max { 137 mg/m³ } → actual case 125 mg/m³ - USA

T_W = 70 mg/m³ – 5hr/day.

(1) O_A – do not agree.

C: Government/Regulators:

– no carcinogenic evidence (danger to human).

(1) – we need more information (to give a limit concentration).

(2). max allow conc in working place, where >40hr/weekly? we need information (long term inhalation)

(3) – only for investigation.

(4) - must be latched
— do not duty.
— keep out from children.

(5) - Do not drink.

CASE STUDY: THE CHRONIC TOXICITY OF HEXANE

(2)
2.12.87

1. Attached are two documents:

   a) an outline of basic information on hexane and it's presumed neurotoxicity in man (background extract from ACGIH documentation).

   b) Summaries of a series of repeated dose toxicity studies in animal species (extracts from Toxicity Review 18, HMSO, pub. November 1987).

2. You are invited to:

   a) assess the studies (as far as possible)

   b) evaluate their relevance to human workplace exposure

   c) suggest (if appropriate) further studies.

DR H P A ILLING

8hr/day

November 1987

Extract from ACGIH documentation.

(A)

HEXANE

CAS: 110-54-3

n-Hexane

$CH_3(CH_2)_4CH_3$

TLV-TWA, 50 ppm (≈ 180 mg/m³)

Normal hexane is a clear, volatile liquid. Its physiochemical properties include:

Molecular weight: 86.17
Specific gravity: 0.660 at 20°C
Solidifies: −95° to −100°C
Boiling point: 68.95°C
Vapor pressure: 124 torr at 20°C
Closed cup flash point: −23°F (−30.56°C)
Explosive limits: 1.2% and 8% by volume in air

Insoluble in water, n-hexane is miscible with most organic solvents and quite soluble in alcohol.

Commercial hexane is a mixture of hexane isomers with small amounts of cyclopentane, cyclohexane, and pentane, and heptane isomer. It may contain as little as 20%, or as much as 80%, of normal hexane. The commercial grades of hexane are used as solvents for vegetable oils, adhesives, etc., and as denaturants for alcohol. The various hexane isomers are present in varying amounts in petroleum ether, rubber solvent and gasoline. According to McDermott and Killiany[1] the average hexane content of vapors encountered in bulk gasoline handling was 5.9% of the total; 1.5%, or slightly over a quarter of the total hexane content, was n-hexane.

Hexane is three times as acutely toxic to mice as is pentane; concentrations of 30,000 ppm produced narcosis within 30 to 60 minutes, and convulsions and death resulted from 35,000 to 40,000 ppm.[2,3] In man, 2000 ppm for 10 minutes resulted in no effects, but 5000 ppm caused dizziness and a sense of giddiness.[4] Drinker *et al* found slight nausea, headache, eye and throat irritation to 1400 to 1500 ppm. Nelson and co-workers[5] found no irritation at 5000 ppm in unacclimated subjects.

The preceding data relate generally to n-hexane, although the purity of the liquid was not always specified.

Volatile petroleum solvents, such as petroleum ether and rubber solvent, which contain various isomers of hexane, as well as other alkanes, have been observed to cause narcotic symptoms, such as dizziness, when concentrations exceed 1000 ppm, but from levels below 500 ppm.

Until recently, chronic intoxication from hexane had not been established. In 1967, Yamada[6] described 17 cases of polyneuritis among workers exposed reportedly to n-hexane. Six worked in laminating plants where concentrations of hexane vapor ranged from 1000 to 2000 ppm. The hexane solvent contained 65% of the normal isomer. Eleven cases were from a pharmaceutical plant where concentrations of hexane (95% n-hexane) were between 500 and 1000 ppm.

Yamamura, in 1969, reported that 93 of 296 workers exposed to hexane in the manufacture of sandals were classified as having polyneuropathy.[7] Exposures ranged from 500 to 2500 ppm, for 48-hour or longer work-weeks. Inoue, reporting on the same study, indicated that some affected workers had exposures to n-hexane below 500 ppm.[8]

Herskowitz *et al*[11] described three cases in 1971 of sensorimotor polyneuropathy in employees of a furniture factory. n-Hexane concentrations averaged 650 ppm.

In 1975 Takeuchi and co-workers[12] found four persons exposed to petroleum benzine to have symptoms of polyneuropathy. The solvent contained 12.5% n-hexane, and the n-hexane vapor concentration in the workroom air probably did not exceed 210 ppm.

Abrittie and associates[13] and Buiatti and co-workers[14] reported upon polyneuropathy among Italian shoe workers. There was a correlation of incidence and intensity of signs and symptoms with the degree of exposure to glue solvents. Abbritti found these solvents to contain chiefly pentanes, hexanes, and heptanes. Buiatti reported that the solvents apparently responsible for 86 cases of polyneuropathy among 338 workers contained 40%-90% n-hexane, 7%-34% other low-boiling hydrocarbons and 7%-10% n-heptane.

No measurements of solvent vapor concentration were reported, but Buiatti noted that 17 of 39 affected workers used less than 1.3 kg of glue per day. Except with extremely poor ventilation, average vapor concentrations in excess of 500 ppm would not be expected from operations involving such quantities of solvent.

Cavigneaux,[15] in 1972, noted the occurrence of numerous cases of (occupational) polyneuritis in several countries, and that in many the incriminating agent was n-hexane in high concentrations.

In 1973 Gaultier[16] reported polyneuritis among workers exposed to the vapors of solvent containing 80% pentane, 14% heptane, and 5% hexane.

While many of the above reports specified n-hexane as the chief, if not the only, solvent used, some[12,13,16] indicate that exposures were to mixtures in which n-hexane was, or may have been, a minor ingredient. It would be unusual, moreover, for n-hexane as such to be used for general solvent purposes. Even a very narrow boiling range solvent would be likely to contain as much as 95% of a single compound. In most instances it is probable that commercial hexanes were used, with normal hexane contents which might vary from 20% to 80%. Details of the analytical procedures in the above reports were not given.

It is not an uncommon practice, when discussing paraffin compounds, to omit any prefix when referring to the normal isomer. Thus, on the one hand, hexane may in fact mean normal hexane, and on the other hand, it may be assumed to be the normal isomer when other hexanes are present and may even predominate.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals	Concentration/dose/ duration/purity	Observations
INHALATION EXPOSURE		
Rat (115, 127) CD(Sprague-Dawley derived) 24 males (0 ppm), 14 males (125 ppm) 34 males (500 ppm)	0, 125 or 500 ppm c.22 hours/day 7 days/week for up to 6 months n-Hexane was 99.3-99.4% pure. A residue containing a phthalate ester type compound was found in the vapour generation system, and originated apparently from the test material	No deaths occurred. Abnormal gait was noted at 500 ppm from week 14. Body weight gain was reduced from week 3 at 500 ppm. Increased relative liver and kidney weights were noted after 6 months' explosure to 500 ppm ($p \leq 0.01$). No toxicologically significant effects were noted on the weights of brain, spleen, heart (plus trachea), lung, testis or adrenals. An extensive pathological examination was conducted after 6 months on 10 rats per group. Treatment-related discoloured and raised/soft areas were noted on the liver at 125 and 500 ppm. Microscopically mild-moderate panlobular liver necrosis was noted in 2-3 rats at both concentrations. Other microscopic lesions noted at 500 ppm were: traces of degenerative and regenerative changes in the kidneys of 4 rats (including respectively caste formation and cytoplasmic basophilia); axonal degeneration (swellings) in the sciatic nerve and lumbar and sacral spinal cord in 7-8 rats, together with minimal myelin vacuolation in the spinal cord in 1 rat; atrophy of gastrocnemius muscle of 9 rats. None of these lesions was noted in control rats. No treatment-related lesions were noted in the many other tissues examined microscopically, including lungs, testis, lymphoid organs, salivary glands and nasal turbinates. The nervous system was also examined by special histochemical techniques (every month at 500 ppm and after 6 months at 125 ppm). At 500 ppm, some axonal swelling was seen in the tibial nerve and brain (medulla oblongata) at 2 months; by 6 months, all animals showed advanced axonal swellings and degeneration in tibial nerve, sciatic nerve, lumbar cord and medulla oblongata, as well as axonal loss in the tibial nerve. No toxicologically significant lesions of the PNS or CNS were seen after 6 months' exposure to 125 ppm or in the control group.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals	Concentration/dose/ duration/purity	Observations
		Co-exposure to 125 ppm n-hexane plus 375 or 1375 ppm n-hexane free hexane resulted in kidney toxicity (increased relative weight and degenerative/regenerative changes).
Rat (116, 127) CD (Sprague - Dawley derived) 20 males/group	0 or 500 ppm C.22 hours/day 7 days/week for up to 6 months Purity and residue as above	One control rat died during week 1 and was replaced with another animal. Abnormal gait was observed in test rats from week 16. Body weight gain was reduced from week 7. Increased relative kidney weight was noted after 6 months' exposure ($p \leq 0.01$). No toxicologically significant effects were noted on other organ weights (organs as above). An extensive pathological examination of 10 rats/group after 6 months revealed no treatment-related gross lesions. Microscopically, mild atrophy of tibial and sciatic nerve fibres was noted in most nerves examined, with mild secondary atrophy of skeletal muscles in 3 rats. These lesions were not seen in control groups. There was also an increase in the incidence and severity of chronic nephritis, but this was considered to be of equivocal toxicological significance. No treatment-related lesions were noted in the many other tissues examined microscopically, including lungs, testis, lymphoid organs, salivary glands and nasal turbinates. The nervous system was also examined by special histochemical techniques. After 2 months, axonal swellings were seen in the tibial nerve, medulla oblongata and more rarely in the lumbar cord. After 6 months, axonal swellings, Wallerian-like degeneration and axonal loss were seen in tibial and sciatic nerves, lumbar cord and medulla oblongata. The tibial nerve was the most severely affected. No lesions were observed in some other areas of the PNS and CNS, including the cerebral cortex and cerebellar vermis. Similar results were recorded following co-exposure to 500 ppm n-hexane plus 500 ppm n-hexane free hexane.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals	Concentration/dose/ duration/purity	Observations
		Thus in this study neurotoxicity was noted following continuous exposure to 500 ppm n-hexane for 2 months. No neurotoxic effects were seen following exposure to 125 ppm for 6 months. No consistently marked effects were noted in any other tissues following exposure to n-hexane.
Rat (117, 131) Sprague-Dawley 12/sex/exposure group	(1) 0, 5 ±1, 27 ±1, 126 ±4 ppm (mean ± S.D.) 21 hours/day, 7 days/week for up to 34 weeks	1 male exposed to 27 ppm died on day 36 and 1 control male died on day 91. No treatment-related gross pathological lesions were noted in the former at necropsy.
	(2) 0, 6 ±1, 26 ±2 or 129 ±6 ppm 6 hours/day 5 days/week for up to 34 weeks Spectrophotometry grade n-hexane was used	No clear signs of treatment-related toxicity were observed; corneal opacity in the high exposure groups was attributed to scheduled eye bleeding. Increased body weight gain was noted in males exposed to 26 ppm. No treatment-related effects on haematology or limited clincial chemistry were noted after 3 or 6 months. The medulla oblongata, cerebellar vermis and tibial nerve branches to calf muscles were examined histopathologically in all groups after 8, 18 and 26 weeks, and in control and high-exposure rats after 34 weeks. Tibial nerve biopsies were also conducted in control and high-exposure rats after 26 and 31 weeks. Lesions clearly due to hexane were absent, however a marginal increase in 'age-related' lesions was noted in the test group. In this study, no clear evidence of n-hexane toxicity was seen at 125 ppm.
Rat (130) Wistar 5 males/group	0 or 850±85 ppm continuously to an aerosol 6 days/week for 20 weeks. n-Hexane of unstated purity	No deaths were reported, and there were no clear signs of toxicity or effects on nocturnal activity during the exposure period. Haematocrit values and serum protein levels were not affected at termination. Histological examination at termination revealed myelin degeneration (including swelling and vacuolation) and slight axon degeneration in the sciatic nerve. Slight atrophy of hind limb muscle and pathological changes in the spleen (increase in giant cell numbers and

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals	Concentration/dose/ duration/purity	Observations
		haemosiderin precipitation) were also observed. No effects on the liver, lungs, stomach, heart, jejuno-ileum, kidneys or testes were noted apart from slight congestion.
Rat (133, 261) Fischer 344 15 males and 15 females/group	0, 3,011 ±3, 6,507 ±3, 10,004 ±2 ppm (TWA±CV) 6 hours/day 5 days/week for 13 weeks n-Hexane was ≥99.5% pure	No animals died during the exposed period. Reduced body weight gain occurred in high-dose males from week 4. No signs of toxicity were noted on ophthalmoscopic or neurological examination. At termination, urine pH was reduced to 6.0 in high dose males (control males 6.9, $p \leq 0.05$); no significant effects on haematology or serum chemistry were noted. Bodyweight relative weights were increased for liver and testes, in high dose males, and kidneys in medium and high dose males. No treatment-related lesions were noted in nervous and other tissues (including liver, kidneys, lungs, testis, lymphoid organs, salivary glands and nasal cavity) onextensive standard histopathological examination of 10 rats/sex/group. The sciatic and tibial nerves and medulla of 5 rats/sex/group were examined by special histopathological techniques. Mild paranodal axonal swellings were noted in the sciatic nerves of 1 medium dose and 4 high dose males; axonal swelling was noted also in the medulla of 1 high dose male. These lesions were only found in less than 5% of the teased fibres examined in each animal. No toxic effects were noted at 3,011 ppm in this study.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals	Concentration/dose/ duration/purity	Observations
Rat (47) Wistar (CPB/WU) 15 males and 15 females/group	0,100, 300 or 900 ppm (presumably vapour) 8 hours/day 5 days/week for 72 weeks n-Hexane was 99% pure	No treatment-related effects on mortality were reported and no signs of neuropathy or statistically significant effects on body weight were noted. Increased performance in a visual descrimination test was noted at 100 ppm (especially during the first half of the experiment) but no other effects were recorded in two other operant behaviour tests. No marked effects on open-field behaviour nor on rotarod or other neurological tests were noted during the exposure period. No effects were revealed by routine urine analysis. At 60 hours after the last exposure, no immunological effects (lymphocyte mitogenic sensitivity) were recorded and there were no marked effects on organ weights (heart, lungs, liver, kidneys, spleen, hypophysis and testes). No treatment-related pathological changes were seen in these organs by light microscopy or following detailed examination of the nervous system by light and electron microscopy (sciatic and tibial nerves, brain and spinal cord). In this study (with no electrophysiological measurements), discontinous exposure to 900 ppm n-hexane for 72 weeks may be considered a no toxic effect level.
Rat (45, 47, 252) Wistar (CPB/WU) 8 males/group	0 ppm; 300 ppm 24 hours/day, 5 days/week; 900 ppm 8 or 24 hours/day, 5 days/week. All exposures were apparently for 20 weeks	Study reported in summary form only. Significant changes in grip strength and peripheral nerve conduction velocity were reported for rats exposed to 900 ppm. The changes were much greater when exposure was for 24 hours/day and were accompanied by clear morphological effects. Further details of the results of this study are expected soon.
Rat (250) Sprague-Dawley 4 males/group	0 or 910 ± 240 ppm (mean ± SD) 6 hours/day, 5 days/week for 4 weeks n-Hexane was of ag purity	Study of effects on the liver. Animals were killed the morning after the last day of exposure. No effects were noted on body or liver weights or on hepatic microsomal protein content or cytochrome P-450 isozyme composition.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals		Concentration/dose/ duration/purity	Observations
			In addition, no effects were observed on the in vitro metabolism by hepatic microsomes of biphenyl, benzo(a)pyrene, 4-androstene-3, 17-dione or 5α-androstane-3α, 17β-diol.
Mouse NMRI 110 test males and 200 controls	(138)	0 or 25,000-30,000 ppm (saturated air) under static conditions 23 hours/day for up to 4 days n-Hexane was Uvasol grade	Body weight was reduced and relative liver weight increased. Hepatic microsomal protein, cytochrome P-450 and cytochrome b5 levels were increased. NADPH-dichlorophenol indophenol reduction, cyclohexane hydroxylation and cyclohexane binding in hepatic microsomes in vitro were also increased. Young mice were used for these experiments because they suffered less than older mice, or rats, or especially rabbits.
Guinea pig 10/test group and 3/control group	(113)	0 or 8,520 ppm (30 mg/1) 2 hours/day for 60 days. Other animals were exposed to 0 or 42,600 ppm (150 mg/1) 2 hours/day for 30 days Hexane of unstated purity	Two animals died during exposure to 8,520 ppm and one during exposure to 42,600 ppm. The deaths were attributed to the infections noted at necropsy. Initial restlessness was observed followed by mild torpor and sometimes dysfunction of the hind limbs; the latter resolved rapidly on removal from the exposure chamber. Signs of irritation of the conjunctival and nasal mucosae were also noted. Histological examination at the end of the exposure period revealed widespread congestion, which was most marked in the myocardium and lungs. Degenerative changes were noted, particularly in the liver (slight vacuolation and regeneration of hepatocytes), brain (sporadic neuronal tigriolysis and vacuolation) and kidney (epithelial swelling in convoluted tubules), but also in the lungs, spleen and adrenals. The pancreas appeared to be normal. It is presumed that all the above effects were seen at both exposure levels, but this was not clearly stated. It is also not clear if intercurrent infection played any part in the pathological changes noted in the survivors.

Table 3: Effects of prolonged exposure to n-hexane (and hexane) in animals

Species/strain/ number of animals		Concentration/dose/ duration/purity	Observations
Guinea pig 10/group	(139)	0 or 5 mg/1 (1,420 ppm) 2 hours/day for 120 days, 30 mg/1 (8.520 ppm) 2 hours/day for 60 days or 150 mg/1 (42,600 ppm) 2 2 hours/day for 30 days Hexane of unstated purity	Haematological and haemopoietic effects were investigated. Results were presented only for observations made at the end of the exposure period. At 42,600 ppm both erythrocyte and leucocyte numbers and haemoglobin values were decreased slightly. There were increases in the proportion of lymphocytes and eosinophils and a decrease in the proportion of neutrophils. In the bone marrow, the numbers of certain immature cells in both the granulocytic and erythrocytic series increased and the numbers of certain mature cells in these two series decreased. At 8,520 ppm, similar but less marked effects were noted as above but none was statistically significant. No effects were noted at 1,420 ppm. Thus, in this study 1,420 ppm was clearly a no-effect level, with the changes noted at 8,520 ppm being of questionable significance.

Hexane

Scientific

1) Can cause PNS effect.

~~Toxicity only~~

TLV - 50 ppm

MEX 200 ppm . STEL

2)

3) - Further examination - species animals.

- handling model.

Regulation:

1) ~~Can say~~

1) Do not extrapolate:

Pur hex (animal) to human (human)

2) Regulate on human PNS.

3) Toxicokinetic in man:

REPEATED DOSE STUDIES

- General screen for toxic effects.
- Obtain a 'no effect level' and dose-response relationship
- May help in deciding an appropriate monitoring/investigation procedures in man.
- Specific follow-up studies may be required to better understand the toxic effects, their reversibility and their relevance to human health.

Sub-acute	up to 28 days
Sub-chronic	90 days
Chronic	6 months or more

Excluding carcinogenicity studies, tests of longer than 6 months duration are claimed not to add to the overall safety evaluation of drugs.

[Lumley and Walker, 1986]

Size of Group (no/sex/dose level)

Rodent	Non-rodent	
5		Sub acute
10	4	Sub chronic
20	4	Chronic

[OECD]

ASSESSMENT AND EVALUATION

- were the choices of species, dose route and level appropriate?
- were they adhered to?
- was the care and observation of animals satisfactory?
- were the measurements 'in-life' and at termination satisfactory?
- what were the effects found?
- no effect level?
- further studies?
- Good Laboratory Practice?

- Check that nominal and actual dose are similar.
- Information on specificity, sensitivity, accuracy and precision of the analyses.

Example

Coefficient of Variation of assay	25%
Measured concentration	0.75 mg/ml
Desired concentration	1.00 mg/ml

Does the measured concentration agree with the desired?

NO EFFECT LEVEL

(NO TOXIC EFFECT LEVEL / NO ADVERSE EFFECT LEVEL)

The maximum dose used in a test which produces no adverse effects.

[OECD]

"The exposure level at which no adverse effects are detected in an animal experiment is often as little as one tenth of the nearest higher exposure level at which minimal adverse effects or effects of doubtful toxicological significance are found".

[Sharratt, 1976]

- Zbinden - 'An old bone of contention'.
- depends on parameters measured in a study.
- is specific to that study.
- is not evidence that 'serious damage (clear functional disturbance or morphological change which has toxicological significance)' occurs at all higher doses.

No of Parameters measured (oral 90 d. rodent study)

Rodent	Non-rodent	
3 x 15 = 45	15 x 3 x 3 = 135	Biochemistry
3 x 6 = 18	6 x 3 x 3 = 54	Haematology
63	189	

Type 1 error

(rejecting null hypothesis when true)

Type 2 error

(accepting null hypothesis when false)

at P = 0.05, we are accepting that a 1 in 20 error rate is likely.

1. Have we an abnormal spread of results in test or control groups?
2. Do the values in test group, although statistically significant against control values fall within the normal range for that strain in that laboratory?
3. Do the extreme values in parameter A correspond to extreme values in parameter B (both indexes for the same function)?
4. Is there a dose - response relationship?

EXTRAPOLATION TO MAN

(i) Inter species variation

(ii) Inter individual variation

(iii) High dose to low dose.

Although a simple mathematical extrapolation between species may be a first approximation, a better understanding of mechanisms may render this inappropriate.

FURTHER STUDIES

TO UNDERSTAND MECHANISMS OF ACTION

(biochemical toxicology, neurotoxicology, etc)

TO IMPROVE KNOWLEDGE ON EXTRAPOLATION

(toxicokinetics and toxicodynamics).

READING LIST

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U.K. DHSS/IPCS Risk Assessment Seminar

CHRONIC TOXICITY

HYDROCARBON SOLVENTS: A CASE STUDY

A.I.T. Walker

U.K. DHSS/IPCS SEMINAR: CHRONIC TOXICITY

Hydrocarbon Solvents: A Case Study.

INTRODUCTION

Hydrocarbon solvents, or petroleum solvents, are light distillates from crude oils that boil between 30 to 300°C. In consequence, these solvents are complex mixtures of hydrocarbons, generally of chain lengths C5 to C12, containing mixtures of paraffins either straight (normal or n-paraffins) or branched-chain (iso-paraffins), naphthenes and/or aromatics, and usually with less than 2% benzene. These solvents are produced to meet performance and physico-chemical specifications, the mixture of components may vary because of the crude oil used or from changes in process conditions. These petroleum solvents consist of hydrogen and carbon alone, not halogens as in, for example, tetrachloromethane or oxygen as in methyl ethyl ketone.

The solvent for the case study is SBP 80/110. SBP, special-boiling point are solvents in the range 30 to 160°C and are classified according to their boiling range, in this case 80 to 110°C.
SBP 80/110 is used mainly as a solvent or a thinner in paints, lacquers and varnishes; as an extraction solvent for oils and fats by the food industry and in cosmetics and pharmaceuticals; quick drying adhesives, coatings and printing-inks.

In this case study, the use or SBP 80/100 as a solvent in paints or for quick drying products will be considered for this risk assessment. The aim is to determine whether an occupational exposure limit can be established for the workplace for SBP 80/110.

COMPOSITION (% vol.)

n-paraffins	:	35, 8% n-hexane, 17% n-heptane.
iso-paraffins	:	20
naphthenes	:	45
aromatics	:	less than 0.1

PHYSICO-CHEMICAL PROPERTIES (at 20°C and 1013 mbar, unless otherwise stated)

physical form	:	liquid
carbon number	:	6-8
density (kg/m^3)	:	718 at 15°C
boiling range (°C)	:	85-108
viscosity (mm^2/s)	:	0.58
vapour pressure (mbar)	:	96
flashpoint (°C)	:	below 0

OCCUPATIONAL EXPOSURE LEVELS

Substance	TLV[(1)]	ppm	mg/m^3
n-hexane	TWA	50	180
hexane, other isomers	TWA	500	1800
	STEL	1000	3600
n-heptane	TWA	400	1600
	STEL	500	2000
n-octane	TWA	300	1450
	STEL	375	1800

(1) Threshold Limit Values and Biological Exposure Indices for 1986-1987. American Conference of Governmental Industrial Hygienists. Cinicinnati, Ohio, 1986.

TWA = time weighted average concentration for normal 8-h workday and 40-h workweek.

STEL = short term exposure limit, 15 min. time weighted average exposure.

Excursion Limit; in absence of STEL short term exposure should exceed 3 x TWA for no more than 30 min. during workday and under no circumstances should they exceed 5 x TWA provided TLV-TWA is not exceeded.

METABOLISM AND KINETICS

These aspects have been poorly studied for hydrocarbon solvents, with no studies being made on SBP solvents. Individual components have been examined, most notably of the paraffin n-hexane, following the discovery of its neurotoxicity and of the aromatics, benzene, toluene and xylene.

Uptake and Elimination

In practical use conditions, the inhalational and percutaneous routes of absorption are the most significant.

The volatile C-5 to C-7 components on inhalation in rats, diffuse rapidly through the lungs into the bloodstream thence to the central nervous system. Elimination of such solvents is rapid, mainly by the respiratory tract. Solvent vapour does not penetrate intact skin, but in the liquid state absorption can be substantial.
In man, about half the inhaled dose of benzene or toluene is absorbed with about 30% being retained and distributed into fatty tissue. N-hexane was absorbed on inhalation at a lower rate of 15% as were iso-paraffins and naphthenes.

Metabolism

The n-paraffins are usually not metabolised and are excreted unchanged. Some undergo part oxidation, in part, the prime example being n-hexane to hexane-2,5 dione, the latter causing the peripheral neuropathy associated with n-hexane.No data are available on iso-paraffins, while limited studies on naphthenes show some oxidation to hexanols. The metabolism of aromatics has been studied but is not relevant to this case study.

TOXICOLOGY

Toxicity data on SBP 80/110 are derived from specific studies and from those on similar substances or from individual components.

Acute Toxicity

Lethal dose data

oral, single administration	LD50, above 7 g/kg (10 ml/kg)
percutaneous, single administration	LD50, above 3 g/kg (4 ml/kg)
inhalational, 4 hours	LC50, 20,000 ppm (83 mg/l)

Signs of intoxication were not observed following oral or percutaneous exposure. During inhalation, lethargy, ataxia, prostration, coma were observed, signs indicating varying degrees of central nervous system depression.
The main hazard from ingestion of SBP 80/110 is aspiration into the lungs and the consequent chemical pneumonitis. This hazard can be anticipated with substances having a kinematic viscosity of 7 mm^2/s or less.

Skin irritation.

SBP 80/110 is moderately irritant to rabbits using the 24 hour occluded (Draize) test. Using the semi-occluded 4-hour test (OECD) irritation is reduced. Repeated or prolonged contact with the skin is expected to give rise to severe skin irritation.

Eye irritation

SBP 80/110 is not irritant in the rabbit eye, but causes an initial pain response.

Skin sensitisation

SBP 80/110, in common with other hydrocarbon solvents, is not a skin sensitiser, Magnusson and Kligman Guinea-pig maximisation test.

CHRONIC, LONG-TERM OR REPEATED EXPOSURE

SBP 80/110 has not been tested. A series of inhalational studies ranging from three to twelve months have been carried on a number of hydrocarbon solvents.

Nephropathy

Nephropathy occurs in male rats exposed for three months to hydrocarbon solvents rich in iso-paraffins or rich in naphthenes.These studies used three atmospheric concentrations 6 hours daily, 5 days a week for 13 weeks.

The renal lesions related to hydrocarbon solvent exposure are intracytoplasmic hyaline droplets, tubular epithelial regeneration and occlusion and distension of the first part of the proximal convoluted tubules of the male rat kidney. This finding has and continues to be the subject of much research. At present a relationship appears to exist between the metabolism of various iso-paraffins and naphthenes and the appearance of a protein, alpha 2 mu globulin, specific to the male rat.

SB 80/110 with a composition of 20% iso-paraffins and 45% naphthenes could be expected to cause this male rat nephropathy. A rubber solvent of similar composition, boiling range 75-125°C, carbon number C6-C7, 3% aromatics, 41% total paraffins and 54% naphthenes did not cause this lesion in rats exposed for 13 weeks.

Neuropathy

A component of SBP 80/110, n-hexane, is known to cause peripheral neuropathy in both man and experimental animals, a finding that will be considered in detail in the following session, see Table 1.

Carcinogenesis

Studies have not been reported on hydrocarbon solvents such as SBP 80/110, only on aromatics such as benzene and other distillation fractions. An inhalation study of two years in rats and mice using unleaded gasoline resulted in nephropathy and tumours in the male rat kidneys, see Table 2.

Mutagenesis

Data are not available for SBP 80/110. In the few studies published, paraffins, naphthenes and hydrocarbon solvents do not show any mutagenic potential.

Teratogenesis

Few studies have been carried out on either hydrocarbon solvents or their main components. None are available on SBP 80/110. The little work available does not indicate that this class of substances are teratogenic, the exception being para-butyl toluene.

Exposure

Data on exposure in the workplace are inadequate for hydrocarbon solvents. In a number of instances, some reports of dizziness and confusion are available. Odour and irritation thresholds in humans have been measured, with the unpleasant odour and irritation determining the tolerable concentration.

APPRAISAL

SBP 80/110 in common with other petroleum solvents is of a low order of acute toxicity. Effects on the central nervous system are found when inhaling high concentrations of hydrocarbon solvents boiling below 200°C, usually accompanied by irritation of the eyes and upper respiratory tract. Skin irritation can occur, especially after prolonged or repeated exposure. Until the early 1970's and apart from the above local effects, hydrocarbon solvents, with the possible exception of benzene, were not regarded as hazardous.

In the late 1960's, **neurological effects** in laminate and sandal workers were reported from Japan, the chemicals involved being unknown at first. In the period 1971 to 1974 similar reports appeared regarding furniture workers and glue sniffers and in 1974 from Italy in shoe manufacturing. The neurological effect was peripheral neuropathy, the solvent involved being n-hexane. At this time, a similar effect was found in printing workers exposed to methyl n-butyl ketone. For both chemicals 2,5 hexanedione change to is the active metabolite. Studies in animals followed using known exposures, with the metabolite being identified. Following this finding, studies on numerous hydrocarbon and other chemical solvents have been completed. The available data indicate that of hydrocarbon solvents, only n-hexane causes peripheral neuropathy.

The solvents syndrome in painters as reported from Scandinavia is not addressed in this case study. The debate regarding methodology, the subjective nature of the findings continues and is not suitable for this assessment which is based primarily on results from experimental animal studies.

Nephrotoxicity in male rats became apparent during the inhalational studies begun in the mid-1970's on hydrocarbon solvents, gasoline and other petroleum products. Studies to screen for this effect have been in progress since 1984 under the aegis of the American Petroleum Industry (API). In addition the origin of the protein present in the male rat is being investigated.Current evidence suggests this phenomenon is confined to male rats, should not occur in man and is associated with hydrocarbon solvents rich in iso-paraffins and naphthenes.

The **carcinogenicity** study of relevance to this case study is that carried out on unleaded gasoline. Nephropathy in the male rats occurred within three months and progressed throughout the study. The tumours present in all treated groups occurred after 18 months exposure, the rats with the tumours surviving to the end of the study. The carcinoma were found in the P3 on pars recta segment of the proximal tubule. This P3 segment in the rat, unlike the human kidney, is a site for metabolising foreign compounds.

ASSESSMENT OF RISK

The three items relevant to this case study are outlined above, namely peripheral neuropathy, nephropathy and carcinogenicity. Studies on the selected solvent are confined to acute toxicity. The longer-term or chronic toxicity aspects of SBP 80/110 in relation to man, given the absence of definitive exposure data and chronic toxicity studies, have to be assessed on the basis of their composition and physical properties. This approach applies to most, if not all, hydrocarbon solvents and establishing an occupational exposure limit, see attachment, is most relevant for assessing the risk in the workplace.

HYDROCARBON SOLVENTS: A Case Study

Table 1. Peripheral Neuropathy

Results from the Inhalational Exposure of Rats to n-Hexane.

Atmospheric conc:ppm	Lengths of Exposure h/d	d/wk	wk	Effect
10,000	8	7	19	positive
1100	24	5	10	positive
900	24	5	20	positive
900	8	5	52	negative
500	24	7	16	positive
500	9	5	30	negative

h/d-hours per day, d/wk - days per week

Table 2. Carcinogenesis

Two year Inhalational Study in F344 Rats (API, 1983)

Concentration ppm	(a) Number of Rats	Renal Tumours	
		male	female
0	200	0	0
67	200	1	0
292	200	5	1
2056	200	7	0

(a) Equally divided as to sex.

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ATTACHMENT

HYDROCARBON SOLVENTS: A Case Study
Establishing an Occupational Exposure Limit (OEL)

The following approach is to be used to establish an OEL for SBP 80/110. The composition, physico-chemical data and established TLV-TWA (ACGIH) are given on pages 1 and 2 of the case study.

- o assume the atmospheric composition to be that of the liquid phase.
- o assume the toxic effects, narcosis and irritation, for the current TLV (ACGIH) for n-paraffins to be additive, with the exception of n-hexane.
- o the toxicity of n-hexane to be considered independent.
- o the TLV (ACGIH) for iso-paraffins, iso-hexanes, is based on the narcosis and irritation of iso-hexanes containing less than 5% n-hexane: assume the effect to be additive.
- o consider potentiation.
- o assume that components without TLV (ACGIH) to be of average and additive hazard.
- o use the following equation.

$$TLV_p = \frac{p}{\frac{f_a}{TLV_a} + \frac{f_b}{TLV_b} + \frac{f_c}{TLV_c} + \ldots \frac{f_n}{TLV_n}}$$

where p = total fraction % solvent with established TLV
where f = fraction of individual constituent, with established TLV
TLV a,etc = established TLV for individual consistuent.

ATTACHMENT CONTINUED)

The approach on page 1 is taken from that outlined by the American Conference of Governmental Industrial Hygienists. Threshold Limit Values and Biological Exposure Indices for 1986-1987, pp 45-47, Cincinnatti, ACGIH, 1986.

"Appendix C"
Threshold Limit Values for Mixtures.

When two or more hazardous substances, which act upon the same organ system, are present, their combined effect, rather than that of either individually, should be given primary consideration. In the absence of information to the contrary, the effects of the different hazards should be considered as additive.

Exceptions to the above rule may be made when there is a good reason to believe that the chief effects of the different harmful substances are not in fact additive, but independent as when purely local effects or different organs of the body are produced by the various components of the mixture.

Synergistic action or potentiation may occur with some combinations of atmospheric contaminants. Such cases at present must be determined individually. Potentiating or synergistic agents are not necessarily harmful by themselves. Potentiating effects of exposure to such agents by routes other than that of inhalation is also possible, e.g., imbibed alcohol and inhaled narcotic (trichloroethylene). Potentiation is characteristically exhibited at high concentrations, less probably at low.

Examples of processes which are typically associated with two or more harmful atmospheric contaminants are welding, automobile repair, blasting, painting, lacquering, certain foundry operations, diesel exhausts, etc.

The following formula applies only when the components in a mixture have similar toxicologic, that is additive effects, and should not be used for mixtures with widely differing reactivities, e.g., hydrogen cyanide and sulphur dioxide.

SPECIAL CASE: when the source of contaminant is a liquid mixture and the atmospheric composition is assumed to be similar to that of the original material, e.g., on a time-weighted average exposure basis, all of the liquid (solvent) mixture eventually evaporates. When the percent composition (by weight) of the liquid mixture is known, the TLVs of the constituents must be listed in mg/m^3.

$$\text{TLV of mixture} = \frac{1}{\frac{f_a}{TLV_a} + \frac{f_b}{TLV_b} + \frac{f_c}{TLV_c} + \ldots \frac{f_n}{TLV_n}}$$

(ATTACHMENT CONTINUED)

Example : liquid contains (by weight):
50% heptane : TLV = 400 ppm or 1600 mg/m^3
1 mg/m^3 = 0.25 ppm
30% methyl chloroform: TLV = 350 ppm or 1900 mg/m^3
1 mg/m^3 = 0.18 ppm
20% perchloroethylene: TLV = 50 ppm or 335 mg/m^3
1 mg/m^3 = 0.15 ppm

$$\text{TLV of mixture} = \frac{1}{\frac{0.5}{1600} + \frac{0.3}{1900} + \frac{0.2}{335}}$$

$$= \frac{1}{0.00031 + 0.00016 + 0.0006}$$

$$= \frac{1}{0.00107} = 935 \text{ mg/m}^3.$$

of this mixture
50% or (935)(0.5) = 468 mg/m^3 is heptane
30% or (935)(0.3) = 281 mg/m^3 is methyl chloroform
20% or (935)(0.2) = 187 mg/m^3 is perchloroethylene

These values can be converted to ppm as follows:
heptane : 468 mg/m^3 x 0.25 = 117 ppm
methyl chloroform: 281 mg/m^3 x 0.18 = 51 ppm
perchloroethylene: 187 mg/m^3 x 0.15 = 29 ppm

TLV mixture = 117 + 51 + 29 = 197 ppm, or 935 mg/m^3.

(ATTACHMENT CONTINUED)

Example : liquid contains (by weight):
50% heptane : TLV = 400 ppm or 1600 mg/m^3
1 mg/m^3 = 0.25 ppm
30% methyl chloroform: TLV = 350 ppm or 1900 mg/m^3
1 mg/m^3 = 0.18 ppm
20% perchloroethylene: TLV = 50 ppm or 335 mg/m^3
1 mg/m^3 = 0.15 ppm

$$\text{TLV of mixture} = \frac{1}{\frac{0.5}{1600} + \frac{0.3}{1900} + \frac{0.2}{335}}$$

$$= \frac{1}{0.00031 + 0.00016 + 0.0006}$$

$$= \frac{1}{0.00107} = 935 \text{ mg/m}^3..$$

of this mixture
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(ATTACHMENT CONTINUED)

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1 mg/m^3 = 0.25 ppm
30% methyl chloroform: TLV = 350 ppm or 1900 mg/m^3
1 mg/m^3 = 0.18 ppm
20% perchloroethylene: TLV = 50 ppm or 335 mg/m^3
1 mg/m^3 = 0.15 ppm

$$\text{TLV of mixture} = \frac{1}{\frac{0.5}{1600} + \frac{0.3}{1900} + \frac{0.2}{335}}$$

$$= \frac{1}{0.00031 + 0.00016 + 0.0006}$$

$$= \frac{1}{0.00107} = 935 \text{ mg/m}^3$$

of this mixture
50% or (935)(0.5) = 468 mg/m^3 is heptane
30% or (935)(0.3) = 281 mg/m^3 is methyl chloroform
20% or (935)(0.2) = 187 mg/m^3 is perchloroethylene

These values can be converted to ppm as follows:
heptane : 468 mg/m^3 x 0.25 = 117 ppm
methyl chloroform: 281 mg/m^3 x 0.18 = 51 ppm
perchloroethylene: 187 mg/m^3 x 0.15 = 29 ppm

TLV mixture = 117 + 51 + 29 = 197 ppm, or 935 mg/m^3.

CHRONIC TOXICITY

- EFFECT - SENSITISATION
- STUDY - LONGTERM (DEFINE PERIOD)

- AIM IS TO DETERMINE EFFECTS FOLLOWING PROLONGED, REPEATED, EXPOSURE

(EXCLUDE CANCER)

DETECT EFFECTS SUCH AS:

- NEUROLOGICAL
- PHYSIOLOGICAL
- BIOCHEMICAL
- HAEMATOLOGICAL
- PATHOLOGICAL

CHRONIC TOXICITY STUDY

DURATION : NOT LESS THAN ONE YEAR

SPECIES : RAT, DOG (MOUSE, MONKEY)

CHOICE OF DOSES :

- TO SHOW A DOSE-RESPONSE (AT LEAST THREE AND CONTROL);
- TO HAVE A NO-OBSERVED- LEVEL;
- TOP DOSE - SOME TOXICITY WITHOUT EXCESSIVE LETHALITY;
- LOWEST DOSE - NO EFFECTS: RELATED TO ESTIMATED HUMAN EXPOSURE;
- INTERMEDIATE - GRADATION OF EFFECT;
- SURVIVAL - HIGH IN INTERMEDIATE LOW AND CONTROL IN RAT;
  - NO DEATHS IN DOGS.

OBSERVATIONS:

- GENERAL HEALTH AND BEHAVIOUR
- BODYWEIGHT AND FOOD INTAKE
- ORGAN WEIGHTS
- HAEMATOLOGY AND CLINICAL CHEMISTRY
- PATHOLOGY, GROSS AND MICROSCOPIC

CHRONIC TOXICITY

FURTHER DEFINITIONS

TOXICITY : INTRINSIC PROPERTY OF A SUBSTANCE THAT INDUCES INJURY.

HAZARD : TOXICITY CAUSED BY KNOWN AMOUNTS UNDER KNOWN CONDITIONS.

RISK : PROBABILITY OF THE HAZARD OCCURRING AT THE EXPECTED EXPOSURE.
(USE, TIME, AMOUNT AND NUMBER EXPOSED)

SUMMARY

"ALL SUBSTANCES ARE POISONS; THERE IS NONE WHICH IS NOT A POISON. THE RIGHT DOSE DIFFERENTIATES A POISON AND REMEDY".

PARACELSUS (THEOPHRASTUS BOMBASTUS VON HOHENHEIM 1493-1541)

CHRONIC TOXICITY

RISK ASSESSMENT

EFFECT DEFINED AT 10 PPM

- WHAT IS PROBABILITY OF SUCH AN EXPOSURE OCCURRING ?
  OR
- WHAT IS POSSIBILITY OF THE EFFECT AT LOWER DOSES ?

EFFECT AT 10 PPM, NO EFFECT AT 1 PPM

- WHAT IS A POSSIBLE SAFE EXPOSURE ?
  DEFINE AN
  OCCUPATIONAL EXPOSURE LIMIT (OEL)
  OR AN
  ACCEPTABLE DAILY INTAKE (ADI)

CHRONIC TOXICITY

THE CASE STUDY

REASONS FOR CHOOSING A HYDROCARBON SOLVENT

- CURRENT, TOPICAL ISSUE
- LONG-TERM EFFECTS, OTHER THAN CANCER
- HIGHLIGHTS RESPONSIBILITIES OF PRODUCERS IN RELATION TO WORKFORCE, OWN AND CUSTOMERS AND TO REGULATORY REQUIREMENTS
- A MIXTURE; THE SIGNIFICANCE OF INDIVIDUAL COMPONENTS
- INCOMPLETE DATA TOXICOLOGICAL AND EXPOSURE
- PROBLEM OF EXTRAPOLATING FROM ANIMALS TO MAN
- PROBLEM OF ESTABLISHING SAFE EXPOSURES
- DEFINE AN OCCUPATIONAL EXPOSURE LIMIT

HYDROCARBON SOLVENTS

CONCERN OVER TOXICOLOGY
FOR LAST DECADE
SINCE HEXANE AND MnBK

COMPLICATED BY GASOLINE
AND KIDNEY CANCER

CONFUSED BY NORDIC PAINTERS
AND THEIR SYNDROME

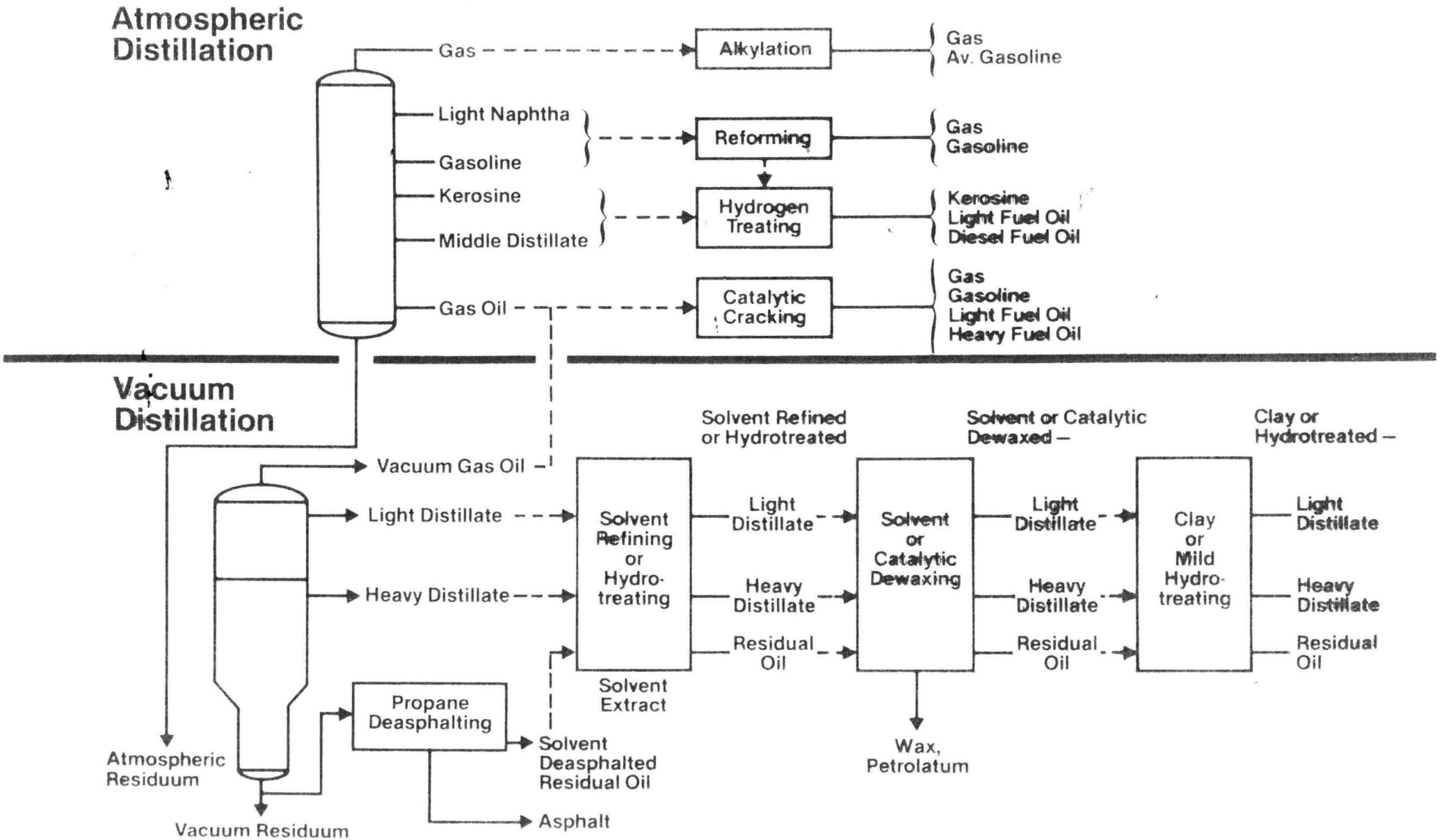
HYDROCARBON SOLVENTS

MISCONCEPTIONS

ALL HYDROCARBON SOLVENTS ARE AS NEUROTOXIC AS HEXANE

ALL HYDROCARBON SOLVENTS ARE AS CARCINOGENIC AS BENZENE

SIMPLIFIED PROCESSING PLAN FOR PETROLEUM REFINERY



HYDROCARBON SOLVENTS

comprise

PARAFFINS , Normal (n-), or straight chain
iso-, or branched chain

NAPHTHENES, cycloparaffins

OLEFINS , both normal - and iso-

AROMATICS , contain the benzene ring

HYDROCARBON SOLVENTS

Paraffin Hydrocarbons

Early Members of Paraffin Series

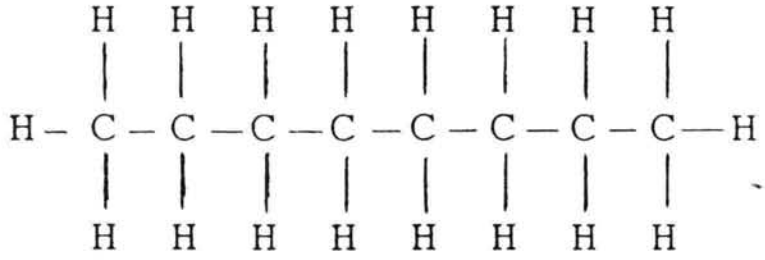
Name	Formula	Boiling Point of n-Parrafin °C	°F
Methane	CH_4	-161.7	-259
Ethane	C_2H_6	- 88.9	-128
Propane	C_3H_6	- 42.1	- 43.8
Butane	C_4H_{10}	- 0.5	30.9
Pentane	C_5H_{12}	36.1	96.9
Hexane	C_6H_{14}	68.7	155.7
Heptane	C_7H_{16}	98.4	209.1
Octane	C_8H_{18}	125.7	258.3
Nonane	C_9H_{20}	150.8	303.4
Decane	$C_{10}H_{22}$	174.1	345.4
Hexadecane	$C_{16}H_{34}$	287.8	550

Melting Point is 18°C (64°F)

HYDROCARBON SOLVENTS

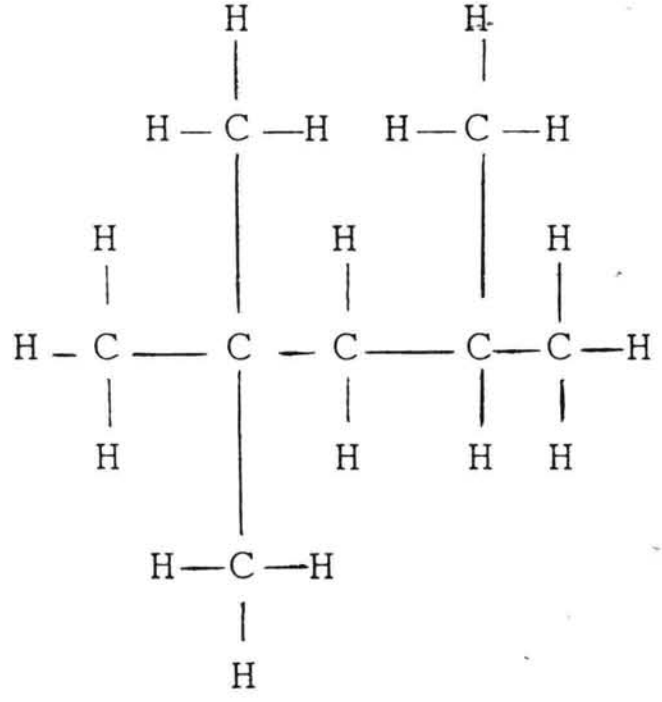
Normal Paraffin

n-octane, $n\text{-}C_8H_{18}$



Iso-paraffin

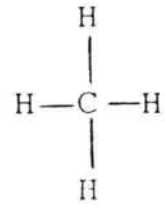
Iso-octane, $i\text{-}C_8H_{18}$



Iso-octane
2,2,4-Trimethylpentane

HYDROCARBON SOLVENTS

Examples of Paraffin Hydrocarbons and their isomers

Name	Formula	No. of Isomers	Stucture
Methane	CH_4	1	

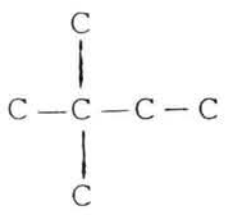
To simplify structures hydrogen atoms are not shown

Butane	C_4H_{10}	2	n-butane  Isobutane
Hexane	C_6H_{14}	5	 n-hexane


2-Methylpentane

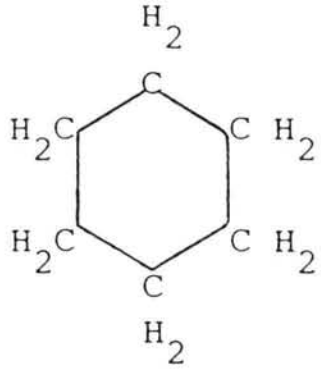

3-Methylpentane


2,3-Dimethylbutane

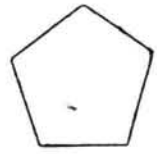

Neohexane
2,2-Dimethylbutane

HYDROCARBON SOLVENTS

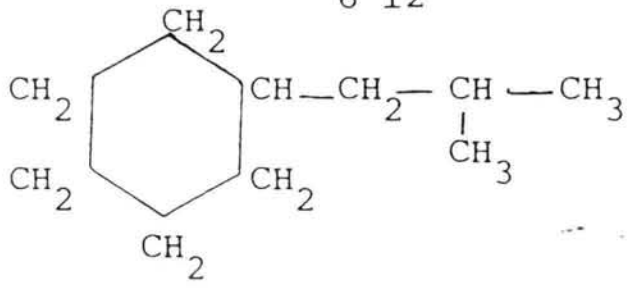
Naphthenes (Cycloparaffins)



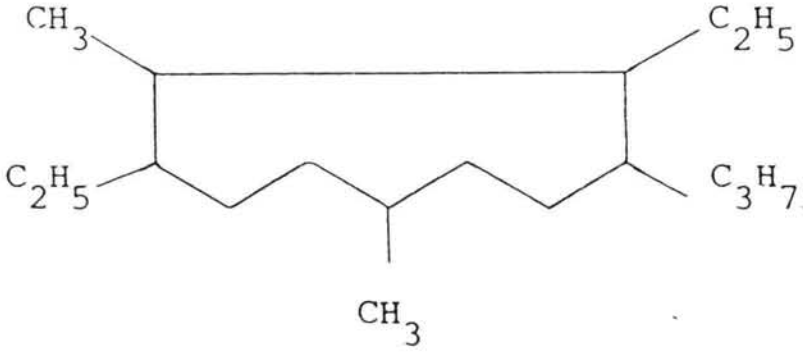
Cyclohexane C_6H_{12}



Cyclopentane
C_5H_{10}



with paraffinic side chain



Possible C_{20} naphthenic oil molecule

HYDROCARBON SOLVENTS

Olefins

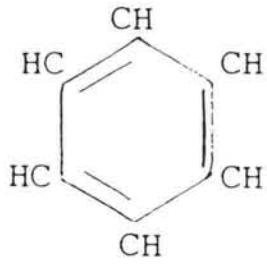
Ethylene , C_2H_4 $CH_2=CH_2$

Propylene, C_3H_6 $CH_2=CH-CH_3$

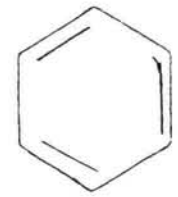
(Alkenes having one double bond)

AROMATICS

contain the Benzene ring

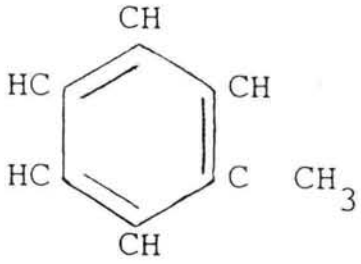


benzene



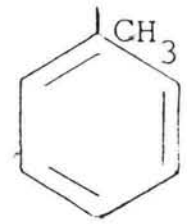
benzene

C_6H_6



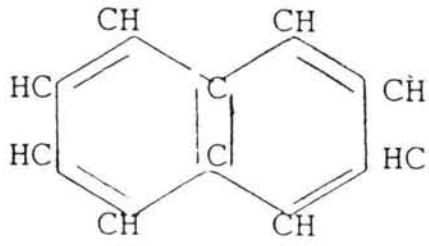
$C_6H_5CH_3$

toluene



Toluene

C_7H_8



$C_{10}H_8$ naphthalene

BLE 2. Composition of typical sample of SBP 80/110[a]

drocarbon ıe	Hydrocarbon	% mass present in sample[b]	Boiling point °C
rmal raffins	*n*-pentane	0.2	36.2
	n-hexane	8.2	69.0
	n-heptane	17.2	98.4
ınched raffins	2 methyl butane T[c]	0.1	27.9
	2,2 dimethyl butane T	trace	49.7
	2,3 dimethyl butane T	0.3	58.0
	2 methyl pentane	1.5	60.3
	3 methyl pentane	1.6	63.3
	2,2 dimethyl pentane	1.0	79.2
	2,4 dimethyl pentane	1.3	80.5
	2,2,3 trimethyl butane T	0.3	80.9
	2,3 dimethyl pentane	9.7	89.8
	3 methyl hexane	9.2	91.9
	3 ethyl pentane	3.1	93.5
	2,2,4 trimethyl pentane	trace	99.2
	2,2 dimethyl hexane	trace	106.8
	2,5 dimethyl hexane	0.6	109.1
	3,3 dimethyl hexane T	trace	112.0
	2,3 dimethyl hexane	0.8	115.66
	3,4 dimethyl hexane	trace	117.7
	3 methyl heptane	0.5	118.9
clo C-6 raffins	cyclohexane	8.4	80.7
	methyl cyclohexane	14.2	100.9
clo C-5 raffins	cyclopentane T	trace	49.3
	methyl cyclopentane	4.7	71.8
	1,1 dimethyl cyclopentane T	2.9	87.9
	1-cis-3-dimethyl cyclopentane T	1.9	90.8
	1-trans-3-dimethyl cyclopentane T	2.7	91.7
	1-trans-2-dimethyl cyclopentane T	0.5	91.9
	1-cis-2-dimethyl cyclopentane T	0.5	99.5
	ethyl cyclopentane	0.6	103.5
	1,1,3 trimethyl cyclopentane T	0.8	104.9
	1-trans-2-cis-4-trimethyl cyclopentane T	0.4	109.3
	1-trans-2-cis-3-trimethyl cyclopentane T	0.4	110.2
	1,1,2 trimethyl cyclopentane T	0.3	113.7
identified raffins		1.1	Probably 110.0
omatic mpounds	benzene	0.7	80.1
	toluene	3.9	110.6
efins		0.4	

From: Shell International Petroleum Co., London (unpublished data).
Average of duplicate analyses.
T = tentative identification.

OCCUPATIONAL EXPOSURE LIMIT
FOR
WORKPLACE
(ACGIH-THRESHOLD LIMIT VALUES: TLV)

14.A Threshold Limit Value - Time weighted Average (TLV-TWA)

8 hour day
40 hour week without adverse effect
50 week year

14.B Threshold Limit Value - Short Term Exposure Limit (TLV-STEL)

15 mins. 4 times per day max.
1 hour minimum recovery
Without exceeding this level at any time
Will not cause irritation
chronic/irreversible changes
impairment by narcosis

14.C Threshold Limit Value - Ceiling (TLV-C)

The concentration that should not be exceeded even instantaneously.

HYDROCARBON SOLVENTS

NEPHROTOXICITY

MALE RATS ONLY

NEUROPATHY

n-HEXANE

NEUROTOXICITY

'PAINTERS SYNDROME'

HAZARD

VOLATILITY

NEUROPATHY

Table 1. Range of Neurotoxic Hydrocarbons

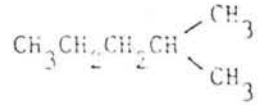
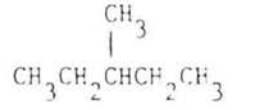
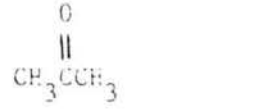
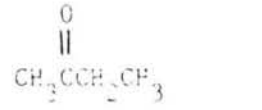
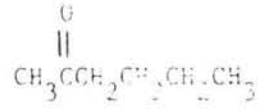
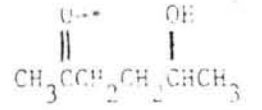
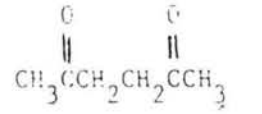
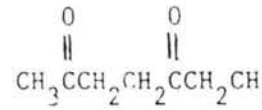
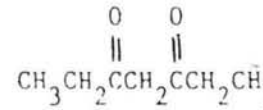
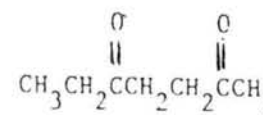
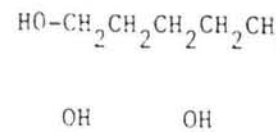
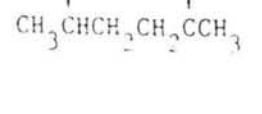
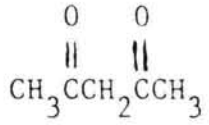
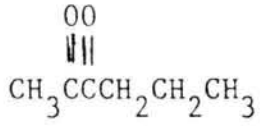
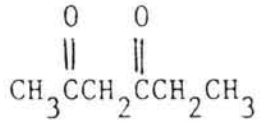
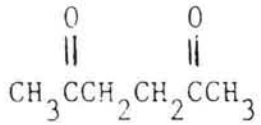
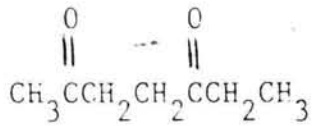
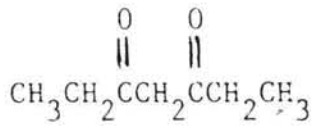
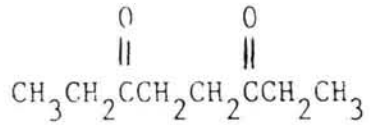
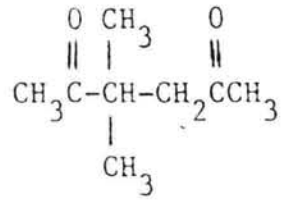
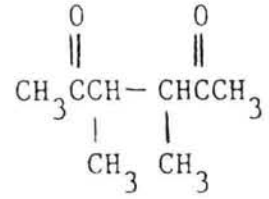
Compound		neurotoxicity
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	+
2-methyl pentane		-
3-methyl pentane		-
Acetone		-
Methyl ethyl ketone		-
Methyl n-butyl ketone		-
5-hydroxy-2-hexanone		-
2,5-Hexadione		+
2,5 Heptanedione		+
3,5 Heptanedione		-
3,6 Octanedione		+
1 hexanol		-
2,5 Hexanediol		+

Table 2. Diketones tested for neuropathy

Diketone	Diketone spacing	neuropathy
2,4-Pentanedione		-
2,3-Hexanedione		-
2,4 Hexanedione		-
2,5 Hexanedione		+
2,5 Heptanedione		+
3,5 Heptanedione		-
3,6-Octanedione		+
3,3-Dimethyl-2,5-hexanedione		+
3,4 Dimethyl-2,5-hexanedione		+

NEPHROPATHY

Table A.I **Petroleum hydrocarbon solvents with prominent nephrotoxic potential, arranged in increasing order of boiling range.**

Product	boiling range °C	carbon* number range	A	n-P	i-P	total P	N
C8 iso-paraffin (Exxon)	98-106	C8	--	--	100	100	--
60 solvent (API)	140-160	C8-C9	49	?	?	30	21
Stoddard solvent (API)	150-195	C9-C11	15	?	?	48	38
High naphthenic solvent (API)	155-185	?	--	19	10	29	70
C10-C11 iso-paraffin (Exxon)	155-173	C10-C11	--	--	100	100	--
dearomatised white spirit (Exxon)	155-193	?	0.5	?	?	52	48
Brightsol (Shell)	156-199	?	2	?	?	35	63
LAWS (Shell)	157-198	C9-C11	19	6	50	56	25
Stoddard solvent (Exxon)	156-204	?	18	?	?	55	27
Shellsol TD (Shell)	168-190	C11-C12	--	--	95	100	--

* = more than 5%
A = aromatics
n-P = normal paraffins
i-P = iso-paraffins
total P = n-P + i-P
N = naphthenics

Table A.II **Petroleum hydrocarbon solvents with dubious nephrotoxic potential, arranged in increasing order of boiling range.**

product	boiling range °C	carbon* number range	A	n-P	i-P	total P	N
VM & P naphtha (API)	125-150	C8-C10	12	?	?	55	33
naphth. arom. solvent (API)	150-200	C9-C11	37	11	14	25	37
70 solvent (API)	155-210	C9-C11	58	?	?	16	16
high arom. solvent (API)	185-205	C9-C11	100	--	--	--	--

Table A.III **Petroleum hydrocarbon solvents without nephrotoxic potential, arranged in increasing order of boiling range.**

product	boiling range °C	carbon* number range	A	n-P	i-P	total P	N
rubber solvent (API)	75-125	C6-C7	3	--	--	41	54
toluene concentrate (API)	95-110	C7	46	13	25	39	15
80 thinner (API)	95-140	C7-C8	71	8	2	10	19
50 thinner	100-105	C7	33	66	--	66	1
mixed xylenes (API)	137-140	C8	100	--	--	--	--
n-nonane (API)	151	C9	--	100	--	100	--
Shellsol A (Shell)	164-184	C9	95	--	--	--	--
140° flash aliphatic solvent (API)	185-210	C5-C12	3	?	?	61	36
40 thinner (API)	185-230	C10-C12	30	?	?	25	44
deodorized kerosine (API)	210-270	?	4	?	?	55	41

* = more than 5%
A = aromatics
n-P = normal paraffins
i-P = isoparaffin
total P = n-P + i-P
N = naphthenics

Table A.IV **Nephrotoxic response in the API 28-day gavage study**

compound	male rat nephropathy
2,3-dimethyl butane	+
2,3-dimethyl pentane	+
2,2,4-trimethyl pentane	+
2,2,5-trimethyl hexane	+
whole unleaded gasoline	+
2-methyl pentane	±
2-methyl hexane	±
2-methyl butane	-
n-pentane	-
trans-2-pentene	-
methyl cyclopentane	-
n-hexane	-
toluene	-
m-xylene	-
1,2,4-trimethyl benzene	-

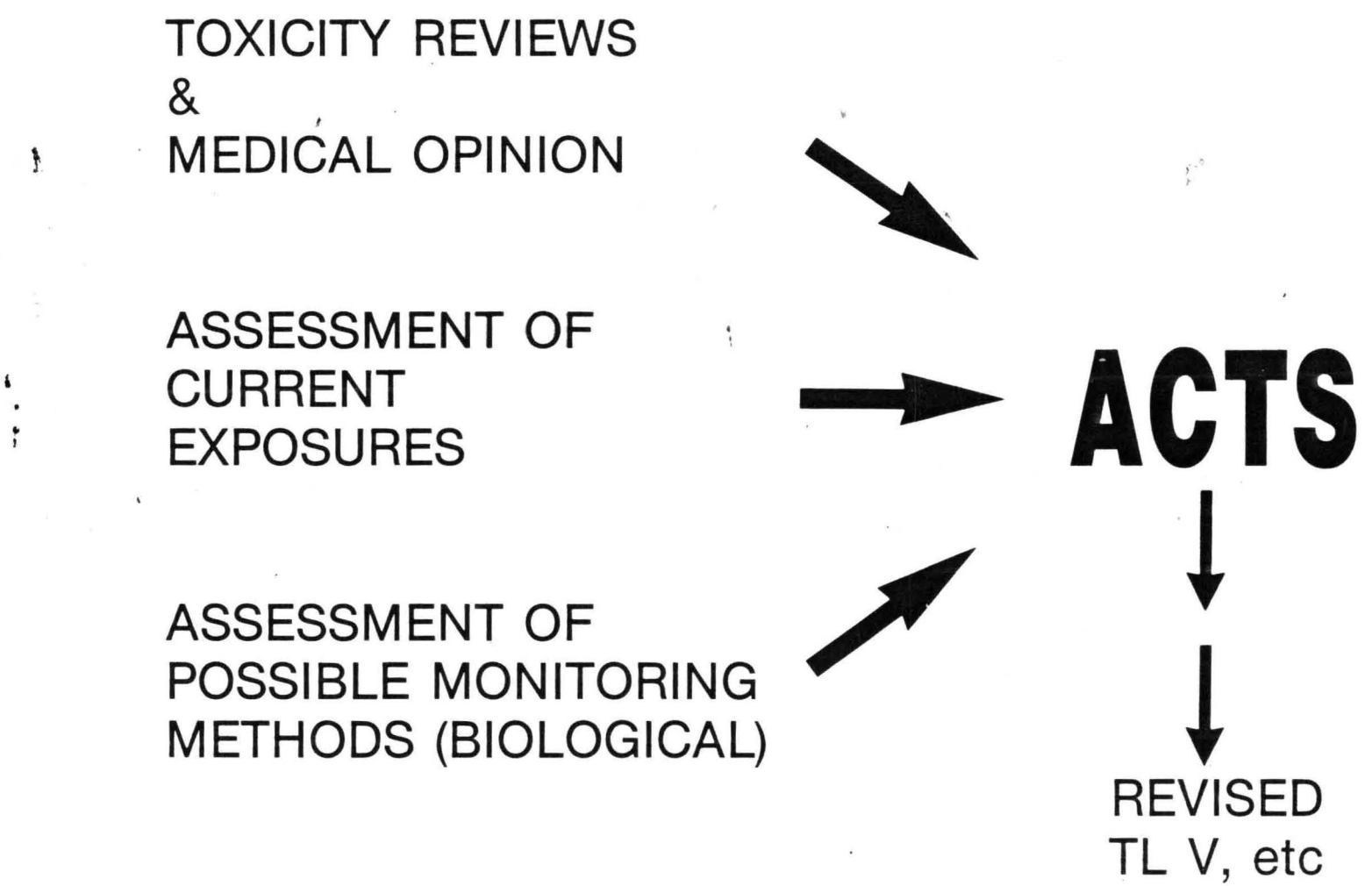
HYDROCARBON SOLVENTS

PERCEPTIONS

UP TO 1960'S	ALL SOLVENTS ARE SAFE
1970'S-80'S	ALL SOLVENTS ARE DANGEROUS ON INHALATION
FROM MID '80'S	SOME SOLVENTS CAN BE HAZARDOUS ON INHALATION

TOXICITY REVIEWS

- Comprehensive reviews of the literature on the toxicity of a particular material, prepared for ACTS as part of the information on the hazards of a compound so that ACTS can assess risk and advise HSC on appropriate Control Limits


TOXICITY REVIEWS
&
MEDICAL OPINION
ASSESSMENT OF
CURRENT
EXPOSURES
ASSESSMENT OF
POSSIBLE MONITORING
METHODS (BIOLOGICAL)
ACTS
REVISED
TL V, etc

Sponsor	Health and Safety Commission	Dept. of Health and Social Services
Name	ADVISORY COMMITTEE ON TOXIC SUBSTANCES	COMMITTEES ON TOXICOLOGY, MUTAGENICITY, CARCINOGENICITY, etc
Composition	Tripartite (Unions, Industry, Experts)	Specialist Experts
Function	Advise HSC regarding risk (what is the maximum acceptable risk [level of exposure] for a substance posing a hazard?)	Advise government, etc regarding the nature of a hazard, based on scientific evidence (is a substance carcinogenic?)

	UK	*US*
MEDICINES	DHSS (Medicines)	FDA
FOOD FOOD ADDITIVES FOOD CONTAMINANTS	MAFF*	FDA
OCCUPATIONAL HEALTH AND SAFETY	HSE*	OSHA
PESTICIDES	MAFF* HSE	EPA (FIFRA)
AIR POLLUTION WATER	DoE*	EPA (TOSCA)

* DHSS—COMA Committees advise on Carcinogenicity, Toxicity, Mutagenicity and Human Health Hazards

MEDICINES ACT 1968

Health and Safety at Work Act 1974

Control of Pollution Act 1974

Foods Act 1984

Food and Environment Protection Act 1985

NEED

Questions in Parliament
Major Disaster

DEFINE SPECIFIC REQUIREMENTS

Committee of Enquiry
Royal Commission
Green Paper

LEGISLATE

White Paper
Bill /Act of Parliament
Statutory Instrument

ENFORCE/MONITOR

MEL
(Maximum Exposure Level)

OES
(Occupational Exposure Standard)

EH 40
(Guidance Note on Occupational Exposure Levels)

CONTROL OF SUBSTANCES HAZARDOUS TO HEALTH

Assessment of risk

Appropriate precautions

CLASSIFICATION, PACKAGING AND LABELLING

New substances

Existing substances

(EINICS lists over 100 000 'existing substances')

NOTIFICATION OF NEW SUBSTANCES REGULATIONS (1982)

NEW SUBSTANCES:

New chemical, not on the market before 18 September 1981 and not recorded in the CEC Inventory

EXCLUDES:

Medicines
Foods/Food Additives etc
Feedstuffs
Polymers
Radioactive Substances
Pesticides
etc. (including non-toxic or very toxic substances of less than 1 tonne)

'BASE SET' DOSSIER

STRUCTURE

PHYSICAL CHEMISTRY

USES

TOXICITY

- ACUTE (2 ROUTES)
- SKIN AND EYE
- SKIN SENSITISATION
- SUB-ACUTE (28 DAY)
- MUTAGENICITY (2 TESTS)

ECOTOXICITY

- DAPHNIA
- FISH

ADDITIONAL STUDIES MAY BE REQUIRED AT **LEVEL 1**

10 tonnes p.a. or 50 tonnes total
e.g. Fertility/reproduction/teratology
sub-chronic/chronic toxicity

and **LEVEL 2**

1,000 tonnes p.a. or 5,000 tonnes total
e.g. chronic toxicology
carcinogenicity
toxicokinetics
2nd species

Both Notifier and Competent Authority are required to discuss what should be done to any specific compound

CONTROL OF PESTICIDES REGULATIONS (1986)

(Joint Technical Secretariat with MAFF)

Based on Expert Committees

- Advisory Committee on Pesticides
- Scientific Sub-Committee

HSE is responsible for

- Wood preservatives
- Public hygiene and nuisance insects not associated with food storage
- 'Other products' for home, industrial or public authority use

TOXICOLOGY FOR MAJOR HAZARDS

What are the consequences of exposure under abnormal conditions?

- concerned (normally) with acute exposure (rupture of tank, etc)
- concerned with delineating safety zones (minimise numbers exposed to 'dangerous doses')
- effects may be short or long term

HAZARD ASSESSMENT

LAB STUDIES

FIELD TRIALS/ENVIRONMENTAL STUDIES

HUMAN STUDIES

NEED DATA ON TYPE OF EFFECT AND LEVEL AT WHICH EFFECT SEEN

ACTION

- Uncontrolled use
- Controlled use
  - limit outlets
  - protective clothing
  - threshold limit values, etc
  - labelling
  - sealed processing
- Complete banning

ENFORCEMENT

ENFORCEMENT

PROFESSIONAL BODIES

- General Medical Council
- General Dental Council
  etc

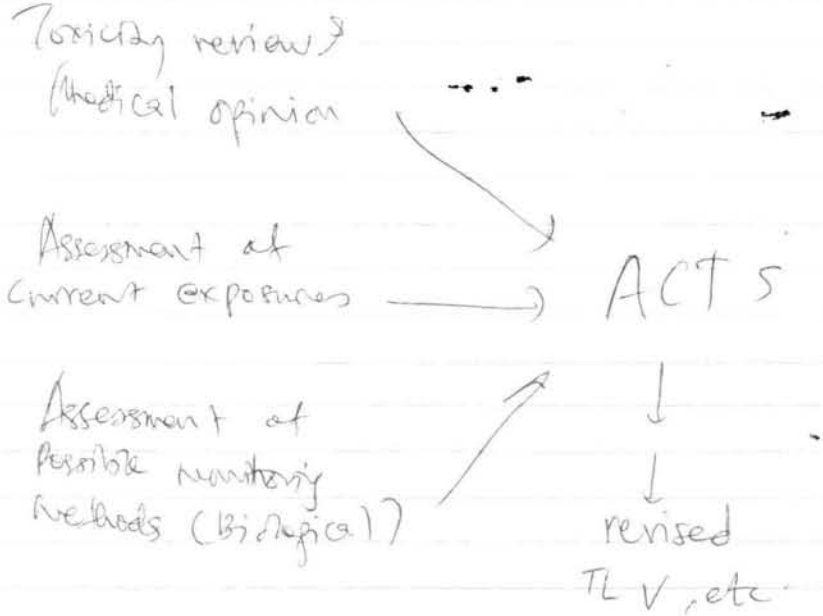
INSPECTORATES/OFFICIALS

HSE - Factory
Agricultural
Mines and Quarries
Nuclear Installations

DoE - Radioactive Substances
Pollution

Local Authority - Environmental Health
- Trading Standards

DT - Railways



Toxicity reviews

- Comprehensive reviews of the literature on the toxicity of a particular hazards, prepared for ACTS as part of the information on the hazards of a compound so that ACTS can assess risk and advise HSE on appropriate Control limits

Reflection and Chronic Toxicity — HPA Illing

Need: Questions in Parliament
Major Disaster

Define specific requirements:
Committee of enquiry
Royal Commission
Green Paper

Legislate:
White Paper
Bill / Act of Parliament
Statutory Instrument

Enforce/monitor

Medicines Act 1968
Health and Safety at Work Act 1974
Control of Pollution Act 1974
Food Act 1984
Food and Environment Protection Act 1985

HAZARD

↓

RISK ----> ----> ACTION

↓

ENFORCEMENT

Assessment and evaluation

- were the choices of species, dose route and level appropriate?
  - were they adhered to?
  - was the care and observation of animals satisfactory?
  - were the measurements 'in-life' and at termination satisfactory?
  - what were the effects found?
  - no effect level?
  - further studies?
  - Good laboratory practice?

- Species
- route of administration and rate
- Stability and homogeneity

- check that nominal and actual dose are similar.
- Information on specificity, sensitivity, accuracy and precision of the analyses

→ does the measured conc. agree with the desired?

Extrapolation is over:

1- Inter species variation.
2- Inter individual variation
3. High dose to low dose

MEL Maximum Exposure Level

OES Occupational Exposure Std.

EH 40 Guidance Note on Occupational Exposure levels

Control of Substances Hazardous to health

Assessment of risk.
Appropriate precaution

Classification, Packaging and Labelling

- New substances.
- Existing substances
- EINICS list over 100000 existing substances

hazards
- acute (24 hrs)
- skin & eye
- skin sensitisation
- sub-acute (28 day)
- mutagenicity (12 tests)

toxicology for major hazards -

What are the consequences of exposure under abnormal conditions?

- Concerned (namely) with acute exposure (rupture of tank, etc)
- Concerned with delineating safety zones, (minimise numbers exposed to dangerous doses).
- effects may be short or long term...

Hazard ast.

1. Lab Policies
2. Field trial / environmental Policies
3. Human Policies
4. Need date on type of effect level.

Action

- Uncontrolled use
- controlled use
  - limit on tests
  - protective clothing
  - threshold limit values, etc.
  - Labelling
  - Sealed processing
- Complete banning

Enforcement.

Inspectors:

HSE – factories
Agriculture
Mines and Quarries
Nuclear ~~(illegible)~~ installations

DOE – Radioactive substances.
Pollution.

Local authority – Environmental Health
– Trading Std.

DT – Railways.

JOHANSOHAIL.

Epoxy Resin.

Monitoring lead exposure.

Env. — airborne (lead)

Biological — blood (lead)

Biological eff. — anemia (ALA)

Diseases — asymptomatic — anaemia.

— symptomatic — constipation
wrist drop.

Asbestos

Lung fibrosis — asbestosis.

test every 2 yrs. { Chest wall fibrosis — Pleural Plaque.

Lung cancer (cigarate). — bronchial

Chest wall cancer — mesothelioma.

1 STH.

1 = SHILLING. =>

J. Spencer

2-12-82.

Worker Surveillance

← Biological Monitoring — detects disease
— Chemical itself.

Health Monitoring

Biological effect monitoring:

Exp. B.M.

Lead — Blood (Lead).
Mercury — urinary (Mercury)
Styrene — Urinary (mandelic acid).
Benzene — Urinary (Phenol)
Trichlorethylene — Urinary [trichloro~~ethyl~~ acetic acid]

Organo Pesticide

Health screening

Asbestos Mica — chest x-ray spirometry.
Isocyanates — spirometry
Epoxies — skin exam
Chrome — skin + nose exam
PCA's — skin exam.
Aniline dyes — urine cytology

408 - Cong

C.B.A = Identification & then Quantification (in monetary Terms).
of all derivable

Identification involves: —
Baseline ?
→ Impact of requirement present scale of problem.
→ Improvement.

Type of Control
- General Duties
(So far as reasonably practicable)
- modification to plant.
- protective equipment.
- test, inspection, medicals
- exposure limit.
- work practices

Type of Risk.
- Cuts & corpses. ←
- Coughs & cancers. - occupational health.
- Catastrophes.

Outcomes
- 1 death in factory accident.
- 1 cancer in >20 yrs.
- 1/1000 apand 1000 ppl.

→ risk & benefit : in all condition we live.

Cost to society.

the overall
test. to see whether one particular project
gain benefit > cost rather than other project.

risk cost benefits to the ~~both~~ whole

DR N J DAVIES

ANNEX A: COST BENEFIT METHODOLOGY

Introduction

A1. The preparation of a Cost Benefit Assessment (CBA) involves the identification and quantification in common monetary terms, of all the desirable and undesirable consequences of a particular measure to the nation as a whole. In undertaking this we are concerned solely with the additional costs and benefits of achieving compliance with any new requirements in the proposed controls not with the costs and benefits of meeting existing requirements.

A2. The purpose of the Annex is to provide a simple guide to the stages involved in this task and the issues that need to be addressed. However CBA is not a standard drill and this is not a comprehensive guide. Policy Sections will need to obtain professional advice from ESU1 before attempting to produce a CBA, except in the most straightforward cases.

A3. Assessing the costs and benefits of a control to the nation as a whole involves attempting to measure the amount of real resources used up (or saved) as a result of that control. This does not mean simply calculating the financial costs and benefits as they fall on or to different groups within the community (such as employers, employees and the public purse) and then adding up the results. One needs to avoid the inclusion in the total costs of financial transfers (e.g. compensation and state benefit payments) and "double counting" (i.e. counting the same resource costs twice as it's successively passed on to different groups within the community). Nevertheless it is important to distinguish the separate effects of controls on the different groups affected (the EDU places particular emphasis upon this).

Identification of Costs and Benefits of Health and Safety Controls

A4. Identifying the costs and benefits of a new health and safety control involves the following tasks:

a. On the cost side

i establishing the "baseline" which is the existing legal requirement, or current practices if higher than this, to compare with the requirements in the proposed control.

ii identifying the additional physical equipment and changes in labour and management practices required and any consequences upon the production of goods and services.

b. On the benefits side

i establishing the present scale of the problem in terms of both actual and potential health detriments.

ii assessing what contribution the proposed control may be expected to have upon this.

A5. Different types of requirement present different problems of identifying the costs and benefits involved. In particular:

i Establishing the baseline is by no means straightforward. The HSW Act general duties require employers to do all that is reasonably practicable to safeguard health and safety. It is often very difficult to identify in what ways the proposed controls go beyond this. To try to do so requires establishing what is presently enforceable, namely what is currently required by inspectors and would be upheld by the courts and is understood to be required by any reasonable employer.

ii Many employers may have already achieved higher standards than those legally required at present and so if a higher legal standard was proposed, compliance with it might involve no additional cost to them. It is necessary to take account of this "prior compliance".

iii Another problem at this stage arises where the proposed control is likely to accelerate the replacement of existing machinery by new plant. It is important not to overestimate the cost of the requirement since economic obsolence would have brought the need for replacement eventually. One also needs to try to identify the other (non safety) gains to firms associated with the new plant.

iv Requirements for the provision of protective clothing/equipment present a different problem at this stage; namely that their effectiveness depends on the extent to which the clothing/equipment is used properly. Experienced inspectors may be able to help here. Otherwise one may need to make a range of assumptions as to the proportion of employees who will use the equipment properly.

v Requirements for routine tests/inspections are likely to have the most important impact on production and hence costs in the form of "downtime". This is the production lost while the machinery is shut down for the inspection. It is hard to assess the impact of this as some inspections may be planned to avoid any output loss (e.g. scheduled during weekends or holidays).

vi Restrictions on the level of exposure to a hazard prescribe the outcome rather than the means of compliance and identifying the costs of compliance will be complicated by the following factors:

- current exposure levels will vary between firms.

- there may be a range of means available to achieve compliance (e.g. engineering controls, personal protection etc).

A6. The problems involved in identification (and subsequent quantification) of the benefits of the proposed control vary considerably according to the type of risk involved. We can crudely categorize the types of risk HSE seeks to control into 3 categories: "cuts and corpses" (i.e. fatal and non fatal workplace accidents); "coughs and cancers" (i.e. occupationally related ill health and disease); "catastrophes" (i.e. the risks from major hazardous installations). ESU1 can advise in each case. The main issues that will be faced in identifying the potential scope for benefit from a control are as follows:

i In the "cuts" and "corpses" situation the main problems involved in establishing the scale of the problem and the scope for improvement from control concern the availability and reliability of sufficiently detailed data. Because their connection with workplace events is usually obvious and immediate, it is possible in principle to observe and record their occurrence. In practice we may not be able to distinguish the injuries we are interested in because we failed to set up a system for this when we set up our record system. Even then the data may be unreliable because it has been recorded and classified incorrectly. It may also be that changes in circumstances (e.g. technological change) make this historic data inaccurate as an indicator of the current scale of the problem.

ii In the "coughs" and "cancers" situation, the problems concerning the availability and reliability of data are intensified. Given the very long time lag that may exist between exposure to substances and the resulting health effects definitive epidemiological evidence may not be available. Such evidence will usually only be available where substantial numbers have been exposed over a long period, and then only if good records have been held. Often the only information will come from experiments on animals from which attempts can be made to derive dose effect curves which can be applied to humans. The uncertainties involved in this are enormous, particularly when it comes to assessing the effect of low levels of exposures. Is the putative dose effect relationship linear? With a suspected carcinogen is it prudent to assume a linear relationship down to zero exposure even if this cannot be established with the evidence that is available? If information about the substance involved is very limited can we make some guestimate of the possible risk at given levels of exposure in relation to some other similar substance whose putative dose effect is better documented?

iii In the case of "catastrophes", Probabilistic Risk Assessment techniques can provide estimates of the present risk drawing upon historical experience, supplemented where necessary by analysis and prediction of potential accidents. These are subject to uncertainties which may be considerable for rare events for which there is little historical record. In such cases a sensitivity analysis (see A26) is particularly desirable.

Quantification of Costs and Benefits of Health and Safety Controls

A7. To assess whether a particular control is worthwhile and to prioritise the regulation of the different hazard we have responsibility for controlling, we need some means of collapsing the various costs and benefits of health and safety controls into a single measure of value. This raises several problems, and in particular:

i The following hypothetical risks are not the same although to some people they might appear to be crudely equivalent:

- one death due to a factory accident.

- one extra cancer case in twenty years time due to exposure to a harmful substance.

- a 1 in 1000 chance of killing 1000 people living and working near a hazardous installation.

ii The most convenient (though not necessarily the only) indication of value is money. Some benefits are easily quantified in money terms, e.g. machine downtime but the main benefit will be in reduced loss of life and limb. How can we place monetary values upon life and good health which is surely priceless?

Putting a Monetary Value on Health and Safety

A8. The traditional approach (adopted by several Government Departments) valued a life as equivalent to the value of a persons future stream of output plus a (fairly arbitrary) sum for "pain, grief and suffering", with a similar approach adopted for valuing non fatal injuries and diseases. For a life this approach produces a value of just over £200,000 (in 1986 prices). This approach has been heavily criticized for failing to take

account of the preferences of the individuals at risk and, in consequence, undervaluing safety. Any value based on this approach should be regarded as the minimum value for a life.

A9. When considering safety measures the choices facing us involve small additional risks of death or other harm to a largish number of people, rather than certain death to a small known population. People do accept risks in return for financial benefits in other situations so, in principle, we can obtain monetary valuation for the additional risks presented by the hazards we seek to control either through:

i seeing what people spend in other situations to reduce the risks they face - the "revealed preference approach" or

ii by asking people what they would spend in hypothetical situations to reduce such risks - the "questionnaire approach".

A10. Examples of the former include estimates of the premia on wages paid for increased risks of fatal accidents after standardizing for numerous other factors that would be expected to influence wages (such as schooling, work experience, unionization and occupational desirability). A recent academic study indicated a value for a life, revealed by differential wages of around £3m in 1986 prices. There have been a number of attempts to obtain values using the "questionnaire approach". A recent study for the Department of Transport obtained values for a life based on individuals stated willingness to pay for transport safety of over £2.5m in 1986 prices.

A11. A related technique has been developed by health economists to put relative values upon different types on non fatal disabilities. This involves the development of a scale ranging from 0 (equivalent to death) up to 1 (equivalent to perfect health). Thus, for example, one year with a disability level rated at 0.5 can be measured as half a "quality adjusted life year" (QALY). This technique therefore aims to equate a given number of non fatal injuries and diseases to an equivalent number of fatalities to which values for a life can be applied.

A12. Within HSE we are still working towards establishing defensible monetary values to apply to health and safety benefits. Policy Sections should consult ESU1 on the appropriate figures to use. Sensitive presentation is essential. Given the uncertainties involved it may be necessary to avoid reference to any explicit values and instead calculate the implicit value that would need to be placed upon a life to equate net present benefits with costs and to compare this with past decisions.

The Use of Opportunity Costs

A13. Most resources have alternative uses in the economy. The cost of using resources in, for example, improving health and safety, is the best alternative use, to which they could be put, that is foregone: i.e. the "opportunity cost". This is the basis used to value resources in CBAs.

A14. The opportunity cost will usually, but not always, be reflected in the prevailing market price. Circumstances where they may not arise where for example:

a. Prices are affected by taxes and subsidies:

Full adjustment of market prices for the distorting effect of taxes is not practicable but it is usual to exclude most indirect taxes. VAT in particular should normally be deducted from the market price of inputs and outputs. No such adjustment should be made for direct taxes (such as income and corporation taxes) nor for import tariffs which are paid to the EEC, nor for property rates.

b. Where there is monopoly:

Profits accruing to suppliers should in nearly all cases be regarded as part of the normal cost of the good or services concerned but this will not necessarily be the case where there is a monopoly involved. However, although excess monopoly profits are not a resource cost, it is usually impracticable to adjust market prices to exclude them.

c. There is substantial unemployment or under employment:

If the unemployed are willing to take jobs at existing wage levels but unable to find them it has been argued that the opportunity cost of employing them must be lower than the prevailing market wages and so a (lower) "shadow" wage used instead. Treasury guidance does not support this argument preferring that such labour market imperfection be dealt with by specific policies rather than through adjusting values used in CBAs.

A15. Resources costs to HSE arise largely from preparation and implementation of new controls. The latter involving inspection for enforcement and, in some cases, administration of notification and licensing systems. Even though no new resources may be made available to implement the new controls there is still an opportunity cost in the form of other work foregone. The resource cost will need to be calculated by applying the Ready Reckoner figures for the cost of the staff involved.

A16. Where new requirements involve diverting labour from productive tasks into training or inspections the resource cost involved is the loss of the output produced by that labour. Since this may be difficult to measure directly it is common practice to proxy the value of the lost output by the cost of the labour inputs (i.e. the wage paid plus other non wage labour costs - national insurance contributions, superannuation etc). This reflects an assumption that the marginal cost of employing labour will equal the marginal product of that labour.

A17. Transfer Payments should not be included. These are payments for which no goods or services are obtained in return. Examples include state benefits and compensation payments. They change the pattern of distribution of income or wealth but do not entail any consumption of national resources (unless of course they are to or from foreign countries or individuals). Transfer payments may be made to compensate for health and safety detriments which, though not resources costs, are nonetheless real costs to those who have suffered harm. However it is not desirable to use such compensation as a proxy for these costs, unless there is no practicable alternative, since they may not reflect the values which the individuals themselves would accept in return for the risk of harm. [See A29 on need separately to distinguish impact on different sectors of the community.]

Welfare Costs

A18. It is important to take full account of losses in economic welfare that may result from control or prohibition of substances. If we control a substance used as an input in the production of goods sold to consumers, the extra costs of producing these goods

will reduce the demand for these goods:

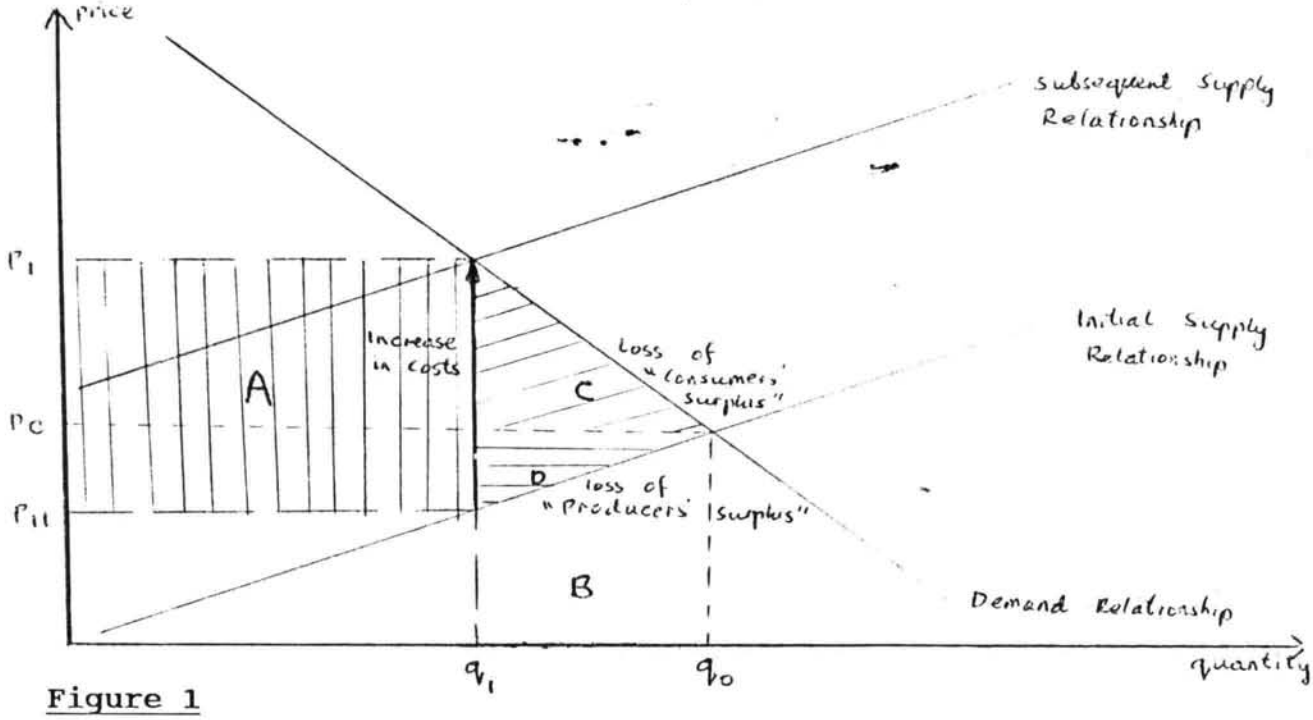


Figure 1

A19. Figure 1 illustrates the impact. The increase in unit costs due to the control is $P_1 - P_{11}$. This will reduce demand and hence sales from q_0 to q_1. The additional resource cost of the control is represented by area A (i.e. the increase in unit costs ($P_1 - P_{11}$) multiplied by the new output (q_1)). This cost is met partially by producers and partially borne by consumers of the final product. However there are two further welfare losses to consider. Firstly there is the loss of producers' profits on the lost output $q_0 - q_1$. This is the lost "producers' supply" represented by the triangular area D. Secondly there is the welfare loss to consumers, represented by the triangular area C. This is the loss of consumers surplus i.e. the extra amount that consumers would have been willing to pay to secure the extra amount of output $q_1 - q_0$. A simple approximation that will usually suffice for marginal changes (and assuming linear demand and supply functions), is that these further welfare effects will be (roughly) half the increase in unit costs ($P_1 - P_{11}$) multiplied by the change in output ($q_1 - q_0$). ESU1 will advise, and where necessary help to estimate these effects. There is also a loss of revenue to producers (represented by area B) but this is fully offset by a saving in resources now available for use elsewhere.

Costs which have already been spent or committed

A20. Costs which have already been spent or committed should not be included because we are interested in the economic impact of the decision under consideration not the impact of past decisions. However account must be taken of the opportunity cost of resources which could still be used for another purpose.

The Time Dimension

A21. Since most people prefer jam today to jam tomorrow, in investment appraisals future costs/benefits are converted into present value through a procedure called "discounting". The discount rate applied to future costs/benefits determines how rapidly the value today of a future £1 falls away through time, just as the rate of interest determines how fast the value of £1 invested now will increase.

A22. HM Treasury recommends a discount rate of 5% per year in real terms be used to reflect the "opportunity cost" of capital i.e. the alternative use of present resources in productive investment.

A23. The application of discounting is sometimes criticized for producing low present values for the benefits of reducing cancers and hereditary effects many years in the future. It is however necessary that appraisal of health and safety controls be undertaken on a basis which is consistent with other public decisions.

A24. Costs and benefits should all be expressed in real terms to remove the effect of future changes in the general price level. However where particular prices are expected to increase a significantly higher or lower rate than general inflation, the relative price change needs to be taken into account in the calculations.

Indirect Effects

A25. A requirement which imposes additional direct costs, e.g. upon employers, can have a number of possible indirect consequences. The cost may be passed on to consumers in higher prices which in turn affect sales, exports and employment. Alternatively it may depress wages or it may reduce profits and investment. The possible indirect effects are complex but may be modelled. HSE however does not have the economist resources to systematically investigate these second round (or indirect) effects. They should not, however, be completely overlooked. We look to both sides of industry to point out possible effects to us during informal or formal consultation.

A26. Even though we aim to quantify and attribute monetary values to all the desirable and undesirable features of the proposal, there will inevitably be factors which cannot be quantified meaningfully. Examples are the assuagement of public anxiety about a potential hazard, the value of better information for employees, emergency services or the general public. These factors should not be ignored but need to be mentioned separately in the CBA.

Sources of Data/Information

A27. To undertake the assessment requires a considerable amount of information and data. HSE has a very wide range of policy responsibility covering a multiplicity of industries. Data collected for one assessment will rarely be relevant to another. The following sources of information and data can be used (though this is not intended as a comprehensive list):

i HSE statistics on occupational accidents and prescribed diseases and various types of enforcement action may help to indicate the size of the problem which new requirements are designed to tackle and in assessing the likely benefits from the controls. The HSE statisticians in ESU2/3 and EMSU should be consulted about what data can be obtained and what interpretation it can support.

ii Other official publications provide data on, for example, earnings (New Earnings Survey, DE Gazette), employment (DE Gazette), non wage labour costs (labour cost survey, DE Gazette), output (Census of Production), and machinery populations (DTI and/or Business Statistics Office Publications).

iii Other Government Departments (e.g. DTI, DE) and Local Authorities are likely to be most useful sources for obtaining unpublished and more detailed data (although there may be problems of confidentiality).

iv HSE Inspectorates and National Industry Groups are a very valuable source of information on existing practices and how the requirements are likely to affect establishments. More detailed quantitative information may be obtained e.g. through planned special visits by inspectors although resources for this are very limited. Even though some inspectorate information may be impressionistic it will provide a solid basis for informing assumptions that one may have to make.

v Trade Associations, Employers Organisations, Chambers of Commerce and Individual Firms are useful sources of detailed information about, for example, numbers of particular types of machines, cost of safety equipment, costs of changes to work practices etc. They may also provide information on possible indirect effects. However there may be problems of confidentiality and information obtained from these sources should not be accepted uncritically.

vi Insurance Companies may provide useful information on numbers and costs of accidents but there are likely to be great problems of confidentiality which may prevent them providing information.

vii Special Surveys may be organised using either postal or telephone interviews or face to face interviewing. However HSE resources for this are very limited and surveys tend to be costly (especially if outside market researchers are used) and burdensome to those surveyed. Furthermore surveys have to be representative and well thought out and executed if the results are to be credible. Surveys should only be considered when an initial assessment indicates that both costs and potential benefits are likely to be substantial and there are significant areas of uncertainty in the initial estimates. ESU3 should always be consulted (see para 30b) when a programme of special visits or survey is considered. They will advise on sampling and questionnaire design and liaise with the survey control unit where appropriate.

Treatment of Uncertainty

A28. Valuing costs and benefits will invariably involve some assumptions having to be made. In some cases the final result may be dependent on the choice of assumptions. This needs to be investigated by varying the assumptions and seeing what happens to the final outcome. This is known as sensitivity analysis. In some cases it may be desirable to provide a range of values rather than a single estimate. It is particularly important to avoid biasing the final outcome through the choice of optimistic assumptions.

The Distribution of Costs and Benefits

A29. CBA is concerned with the best use of the nation's resources not with their distribution. However the costs and benefits of health and safety requirements generally fall upon different parties, and in very different ways within non homogeneous groups. There are therefore important distributional questions that must also be considered by decision makers. It is important that the CBA does not obscure this and presentation of the results should distinguish the impact upon HSE and other public bodies and also the impact upon small and medium sized enterprises (whose viability may be particularly affected by additional Government regulations).

Presenting the Results

A30. The exact form of presentation will vary but, except in very simple cases or in summaries of CBAs, one should aim to set out the following:

i the scope of problem and objectives of the proposal.

ii present requirements and current practices.

iii the resource cost (to the nation) of these requirements (itemized by requirement to help decide whether every requirement is necessary and separating out the costs to HSE and other public bodies).

iv the health and safety benefits in monetary values where possible.

v other benefits (these will generally take the form of cost savings from deregulation aspects of the proposal).

vi comparison of costs and benefits (in net present values) - mentioning any unquantifiable costs and benefits.

vii appraisal of uncertainties.

viii impact upon small and medium sized enterprises.

DR N V DAVIES

CASE STUDY OF ECONOMIC ASSESSMENT

(A) Proposal - to prohibit the industrial use of substance M.

(b) Background - substance M is used in the production of a range of industrial sealants (Y). Test data suggest that M is carcinogenic in the animals tested. But there is lttle epidemiological evidence for humans. You are asked to assess the economic consequences to society of a total prohibition of the industrial use of M. Higher cost alternatives to M are available in some applications.

(C) Health Risk in Animals

1. Acute toxicity

The results of clinical tests on M are as follows: An LD_{50} value of 750 mg/kg in rats was noted for M dissolved in arachis oil. No signs of toxicity was noted at dosages of 5,000 mg/kg in aqueous suspension. In the dog, signs of toxicity, including weakness, cyanosis, pallor and methaemoglobinaemia, were noted after doses of 40 and 80 mg/kg.

2. Sensitivity

Only mild irritation was noted when solutions of up to 40% M were applied to intact guinea-pig skin. Other tests of sensitivity have shown similar results.

3. Sub-acute toxicity

Rats given doses of 200 mg/kg over 2 weeks developed pallor and signs of discomfort, and showed reduced weight gain. Some methaemoglobinaemia was observed and ectopic blood formation was noted at autopsy. In dogs, signs of weakness, pallor, cyanosis and vomiting were seen when the animals were dosed over a 70 day period. Macrocytic anaemia and methaemoglobinaemia were also noted.

4. Mutability

In a number of short term tests, M or it metabolites, has caused point mutation and chromosonal damage in a variety of organisms.

5. Carcinogenicity

Studies using mice, rats and dogs have in all cases produced an increased incidence of malignant tumours. In one study a dose related response was observed.

(D) HEALTH RISKS IN HUMANS

1. There is little data on the effects of exposure to M on humans. Despite considerable use over many years, there are no reports of eye and skin irritation. This suggests M is not a potent skin irritant in man. Mild and transient urinary symptoms have been reported from workers exposed to M, and other chemicals. Similarly, a significantly higher incidence of bladder cancers has been recorded in a group of workers exposed to M, and other substances. In neither case has M been isolated as the causative agent.

(E) AVAILABLE DATA ON SUBSTANCES M AND Y

1.	No of Firms producing substance M in UK	-	1
2.	Total employment in production of substance M	-	25
3.	Production of substance M for domestic use	-	46 tonnes
4.	" " " " for export	-	181 tonnes
5.	Total value of sales of substance M	-	£1 million pa
6.	Annual wages and salaries bill for producing substance M	-	£296,000

7. Substance M is a valuable by-product from a complicated chemical process where the following are also produced -

(a) Substance Q - value £2.5 m per annum

(b) " A - " £0.8 m " "

(c) " O - " £0.7 m " "

8. The annual loss of profits to shareholders of the manufacturer, and the two importers of M amount to £1,000,000.

9. Total employment in production of M and outputs using M is 298.

10. The value of output of Y has increased over the last 4 years. This has largely been the result of a fall in the price of M, which has been passed on wholly to the consumers of Y. The changes in price and value are set out below -

Year	Value of Y in £1000's, at 1986 prices	% charge in value	Price of Y £/tonne
1983	590	-	5.40
1984	660	+11	5.25
1985	750	+13	5.00
1986	1,000	+13	4.00

11. The cost of using the various substitutes for M is approximately £1.80 per tonne; a cost that would be passed onto customers. Because of the costs of transport, there is little international trade in M. 95% of M sold here is made in the UK.

12. The excess mortality associated with exposure to asbestos is 0.3% ie. if 1000 people were working with asbestos, then 0.36% of 1000, that is 3.6 lives would be saved by its prohibition.

(F) OTHER DATA

1. The present value of £1 this year, and every year for the following 10 years is (at a 5% discount rate) £8.722.

2. The equivalent value in 30 years time of £1 today is £4.3215, (at a discount rate of 5%).

3. The value of lost future output associated with early death due to industrial accident or disease is estimated to be an average of £150,000 per case. Average minimum estimated value of compension for pain, grief and suffering associated with early death is around £60,000.

CASE STUDY - ANSWER

COSTS

Two markets are involved: the one for M and the one for Y.

The Market for M

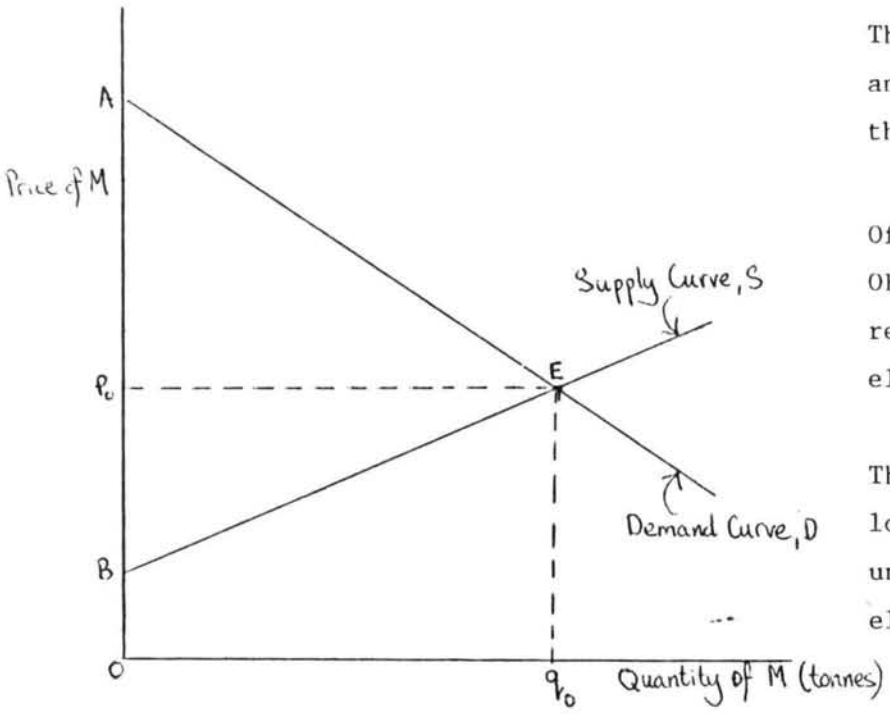


Fig 1

The revenue from manufacturing and importing M is given by the area P_oEq_oO

Of this, the revenue lost $OBEq_o$, is exactly offset by resources freed for use elsewhere.

The area BEP_o, represents a loss to producers, uncompensated by gains elsewhere in society.

This producer surplus (PS) had previously been reflected in the companies' share value. Its size is reflected by the estimated change in the stock market valuation that would result from the prohibition of M. Alternatively, we could look at changes in profitability, that would result.

The area AP_oE represents the consumer surplus, ie the amount consumers would be willing to pay but do not. With the prohibition of M this consumer surplus is lost.

However, the consumers of M are the producers of Y. Their consumer surplus in M is embodied in the costs of production of Y. Therefore, to include lost consumer surplus in the M market would lead to double counting when the market for Y is examined.

The Market for Y

The supply relations and demand relation in the market for Y is represented in Fig 2. The welfare cost of prohibition of M, leading to substitution, is the area $P_1E_1E_oCA$.

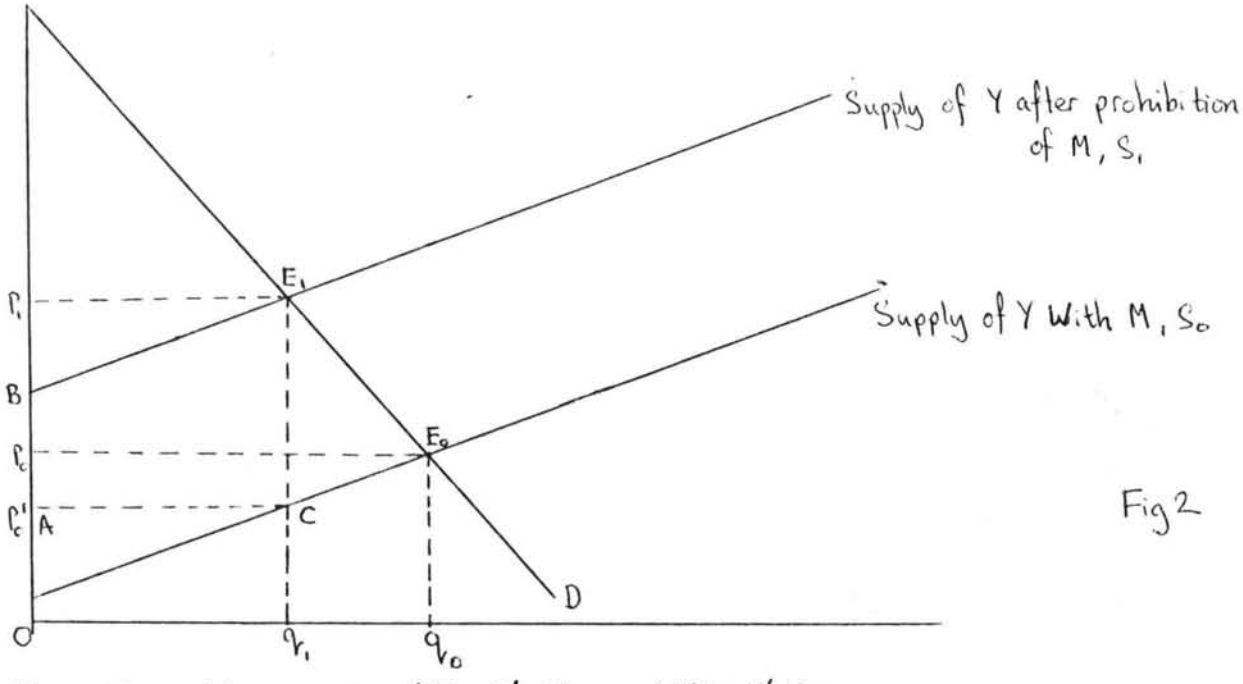


Fig 2

Thus, the welfare cost = $\frac{1}{2}(P_1-P_o')(q_o-q_1)+(P_1-P_o')q_1$

$\frac{1}{2}(P_1-P_o)$ = £1.80

$$q_o = \frac{100}{4} = 250{,}000 \text{ tonnes}$$

$$q_1 = \frac{750{,}000}{5} = 150{,}000 \text{ tonnes}$$

$\therefore$ welfare cost = ($\frac{1}{2}$ x 1.8 x 100,000) + (1.8 x 150,000)

= 360,000

ie = £360,000 per annum

TOTAL COSTS: The total costs, assuming all types of Y can be produced from alternatives to M; and no other costs from switching from M:
is: PS. + £360,000 per annum.

If, PS is assumed to be £100,000 per annum.

Sohaili

Then, total costs = £460,000

The present value of £1 given this year, and for the next 10 years is £8.722.

Similarly, $460,000 over this and the next 10 years has a present value of £4.012 m.

BENEFITS: (1) Estimated number of lives saved that would be sufficient to justify costs of prohibition.

(2) Estimated value of life that would justify prohibition.

(1) Assume that the mean time lag from exposure to M, and health detriment is 30 years.

The present value of the cost of prohibition = £4.012 m

£1 now is equivalent to £4.3215 in 30 years time

∴ number of lives saved would equate benefit and cost = $\frac{17.338 \text{ m}}{.2 \text{ m}}$

= 87 lives

(2) Assume excess mortality rate for M is the same as that for asbestos, ie .36%.

No. workers in contact with M = 344

∴ no. lives saved by prohibition in 30 years time = $344 \times \frac{.36}{100}$

= 1.238

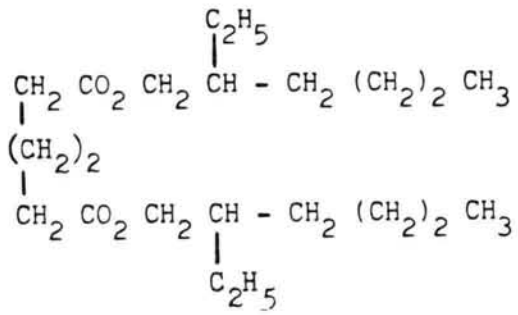
∴ costs of prohibiting M equals benefits if a life is valued at $\frac{17.338 \text{ m}}{1.238}$ = £14.004 m

Disc No 583/38 BH

CASE STUDY - PHTHALATE ESTERS

1. You should consider the evaluation carefully. Do you agree with the arguments proposed and, if you do not agree, what would your conclusions be and why?

2. The plasticizer di(2-ethylhexyl) adipate (DEHA) is widely used in plastic film for food wrapping. The structure is shown below:



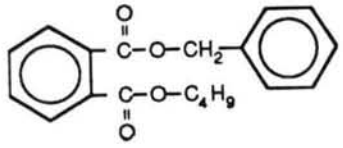
This compound is generally non-mutagenic. In the rat it induced peroxisome proliferation when given in the diet at a levels of 2.5-2%, for 2- for 3 weeks. No peroxisome proliferation was seen in hamsters or marmosets. In a carcinogenicity study in the rat, levels of up to 25000 ppm were given for 2 years but no increased incidence of any tumour type was seen. In the mouse, a marginal increase was seen in males given 25000 ppm DEHA for 2 years (Table 1). How would you interpret these findings?

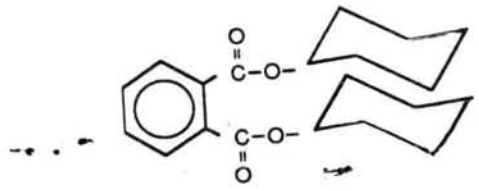
Table 1. Hepatocellular tumours in mice given dietary DEHA

	Male			Female		
	control	low level	high level	control	low level	high level
number of livers	50	49	49	50	50	49
hepatocellular						
adenoma	6(12%)	8(16%)	15(30%)	2(4%)	5(10%)	6(12%)
carcinoma	7(14%)	12(24%)	12(24%)	1(2%)	14(28%)	12(24%)
mice with primary liver tumours	26%	41%	56%	6%	38%	37%

3. What regulatory action would you take on DEHA and why?

4. New plasticizers based on o-phthalic acid are continually being developed. Examples of existing materials are benzyl butyl phthalate and dicyclohexyl phthalate (over leaf).





If you were given the problem of deciding on a priority list for toxicology studies on a new phthalate ester, what would you choose, and why?

5. The properties of hypolipidaemia/peroxisome proliferation/ carcinogenicity in animals are seen not only with phthalates but also with certain compounds used clinically as hypolipidaemic drugs. Examples are clofibrate and fenofibrate. If you were asked as a regulator to decide whether or not a new hypolipidaemic agent should be marketed, what would you wish to know about its toxicity? If marketing was allowed, what might you do to ensure that the compound was safe in humans?

DEHP

- can be hazardous to man
- the MTD is not significant for man
- there is no clear-cut evidence for carcinogenesis in animal (rodents)
- wide spread contaminant
- not genotoxic
- hepatic peroxisome has no clear mechanism

- experiment should be improved
- further experiment

CASE STUDY - PHTHALATE ESTERS

1. Introduction

Phthalate esters are derivatives of o-phthalic acid (I, Figure 1) that are widely used as plasticizers. Plastic materials such as polyvinyl chloride (PVC) would ordinarily be difficult to work (roll, mould etc) and would be extremely brittle. Such plastics are rendered more flexible by the addition of compounds known as plasticizers. Of these the most commonly used are the phthalate esters of which di (2-ethylhexyl) phthalate, usually known as DEHP (V, Figure 1) is the most widely employed.

2. Physical/Chemical Data

DEHP ($C_{24}H_{38}O_4$, molecular weight 390) is a colourless or yellow, oily liquid of low volatility at room temperature. It has the following physicochemical properties:

melting point $-50^{\circ}C$

boiling point $370^{\circ}C$ (atmospheric pressure)

$231^{\circ}C$ (5 mm mercury, 6.67×10^{2} Pa)

specific gravity 0.986 ($20^{\circ}C$)

flash point $425^{\circ}C$ (open cup)

vapour pressure 3.4×10^{-7} mm Hg (4.53×10^{-5} Pa)/$25^{\circ}C$

0.001 mm Hg (1.3×10^{-1})/$100^{\circ}C$

octanol/water partition coefficient log $P_{o/w}$ 3-4

Its solubility in water is low (0.3-0.4 mg/l at 20-25°C) but it is miscible with most common organic solvents. Like most simple esters it has low chemical reactivity.

3. Kinetic and Metabolism Data

DEHP is rapidly absorbed from the gastrointestinal tract of the rat and pig after oral dosing. In the rat, around 80% of a single oral dose was excreted in the urine indicating extensive absorption. However, in the marmoset only around 2% of an oral dose was absorbed.

DEHP is rapidly hydrolysed *in vivo* in a variety of species to its monoester, mono (2-ethylhexyl) phthalate (VII, Figure 1) and the alcohol, 2-ethylhexanol. MEHP is extensively oxidised to yield a number of hydroxylic and carboxylic derivatives (Figure 1) whilst the 2-ethylexanol is converted to ketones (e.g. 2-heptanone) and other oxidative metabolites and eventually to carbon dioxide.

Distribution occurs to most tissues with the highest levels being seen in the liver. Fatty tissues show a preferential uptake but levels rapidly decline once compound administration is stopped.

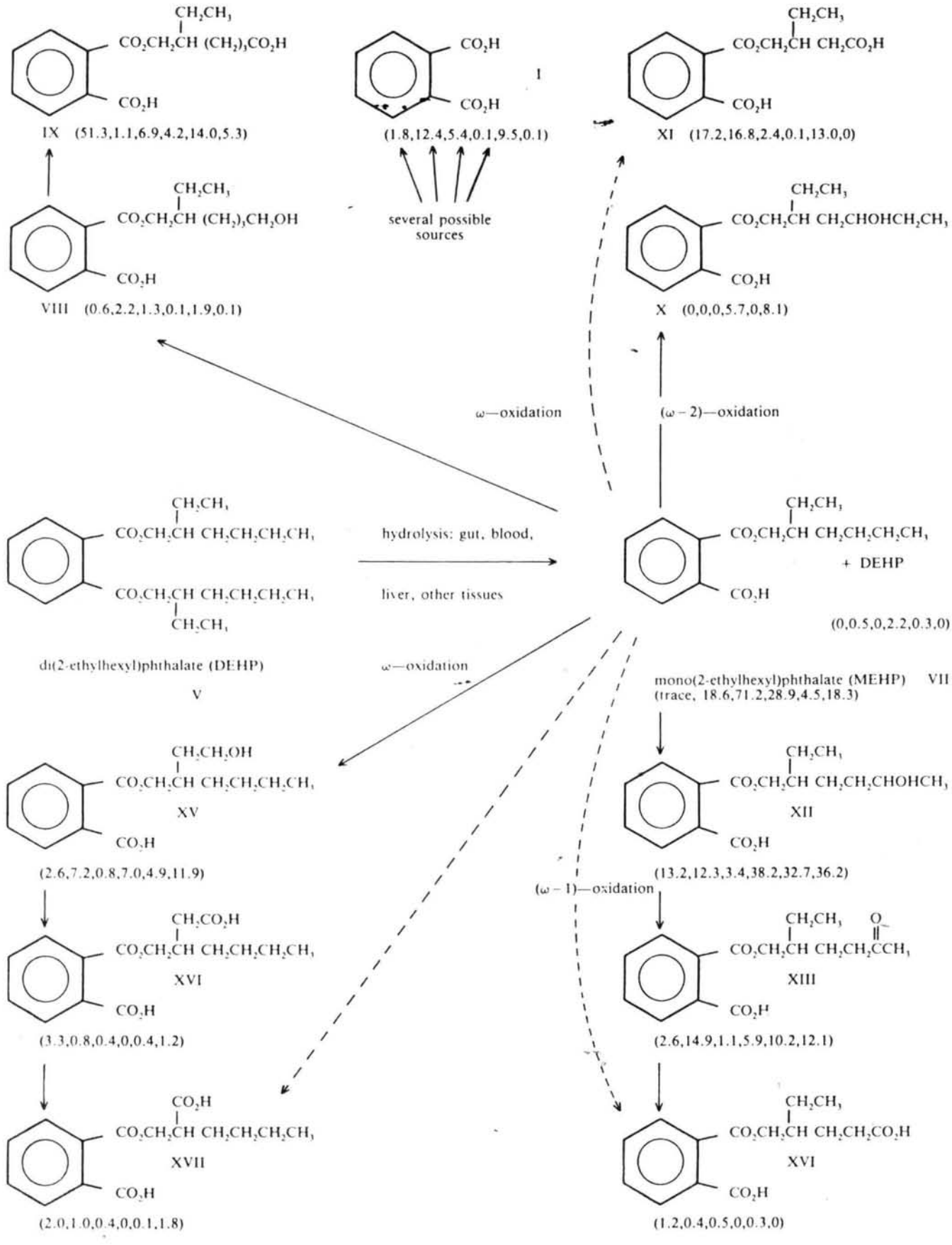


Figure 1 The identities of the urinary metabolites of DEHP and their relative excretory patterns. Figures in parentheses are for: rat, mouse, guinea-pig, African green monkey, hamster and man* showing the percentage of total urinary metabolites.

* After intravenous infusion.

DEHP and its metabolites are rapidly excreted in the urine of rats and mice after oral (or intravenous) administration. Some faecal elimination resulting mainly from biliary excretion (rather than from non-absorption) also occurs. In the marmoset however where poor absorption occurs, the majority of an oral dose is excreted in the faeces.

In humans after oral dosing, absorption occurs and DEHP and its metabolites are evident in the urine. Similarly, DEHP and its metabolites are excreted via the urine after intravenous (often inadvertant) administration. DEHP is rapidly hydrolysed in humans and a variety of metabolites derived from the oxidation of MEHP have been identified (see Figure 1). Distribution to all tissues occurs with high levels being noted in the liver and fat. Excretion is rapid and mainly urinary.

4. Toxicity Data and Toxicity Evaluation

An enormous amount of research has been directed towards a better understanding of the toxicity of DEHP and its metabolites. Most of this work has been conducted in rodents but occasionally other species have been used, including primates.

a. General Toxicity

i) acute toxicity. DEHP has low oral toxicity in mammals. The LD_{50} value is in excess of 25 g/kg in rodents. The compound also has low toxicity after intraperitoneal administration with LD_{50} values of 37 g/kg being reported for the rat.

Following intravenous administration as the undiluted substance or as an emulsion the toxicity is again low but if given in solubilised form such as in Tween 80, a much higher degree of toxicity was reported. A phenomenon known as "shock-lung" developed charaterised by oedema, haemorrhage, and infiltrations of polymorphonuclear leucocytes. In the rat, LD_{50} values of 200-250 mg/kg were calculated. Similar effects were noted in beagle dogs given 300 or 1,000 mg/kg solublised DEHP but not in those given 100 mg/kg or below.

ii) irritancy

No signs of irritancy were noted in guinea-pig or rabbit skin after topical treatment with DEHP. DEHP was not irritating to the rabbit eye.

iii. sub-chronic toxicity

After sub-chronic administration of DEHP to laboratory animals two major effects have been reported namely, those on the testes and liver.

- effects on the testes

rat

Oral doses of DEHP produce testicular atrophy in the rat. This is characterized by a reduction in testicular weight, and a uniform atrophy of the testes with loss of advanced germinal cells. Only Sertoli cells and some primary spermatocytes remain. The doses used have often been high - in excess of 1,000 mg/kg or 1% in the diet with dosing periods of 4 days to 21 weeks.

other species

Mice and hamsters are more resistant than the rat to the testicular effects of DEHP. Dietary levels of up to 25,000 ppm for 13 weeks had no effect on the mouse testes whilst 4.2 g/kg DEHP for 9 days to hamsters produced mild atrophy in only 2/7 animals. The marmoset was also resistant; oral doses of 2,000 mg/kg for 14 days did not produce any testicular effects.

- effects on the liver

rat

Hepatomegaly is seen in rats after administration of DEHP, and this is accompanied by a proliferation of the cellular organelle known as the peroxisome. (Peroxisomes appear to have several functions but the major one is the B-oxidation of fatty acids). This is accompanied by elevations in the activies of peroxisomal enzymes, particularly in those of catalase and carnitine acetyltransferase. Peroxisomal B-oxidation is greatly enhanced. Accompanying the hepatic changes, and probably related - at least in part, is a hyperlipidaemia with decreases in plasma triglycerides and cholesterol. The no-effect level is not known with certainty but appears to be around 10 to 50 mg/kg/day.

other species

Mice are also susceptible to the hepatic effects of DEHP but hamsters and marmosets appear resistant. Doses of up to 1,000 mg/kg for the hamster or 2,000 mg/kg for the marmoset, both for 14 days, produced no detectable hepatic effects.

b. Reproductive Effects

i. teratogenic effects

rat

Doses of up to 1.7 g/kg/day DEHP throughout gestation led to reduction in fetal weights. Dietary levels of 2% DEHP produced increased incidences of resorptions but no fetal malformations.

mouse

Levels of 0.1 % DEHP in the diet throughout pregnancy produced embryolethality and increased the incidence of malformations (mainly spinal and tail anomalies). The most sensitive day of gestation was day 7; oral doses of 50 mg/kg on this day led to reduced fetal weight in the absence of maternal toxicity.

ii. effects on fertility

rat

DEHP, 0.34 or 1.7 g/kg to female rats, for 3 months prior to mating had no effects on the numbers of resorptions, live or dead fetuses, fetal weights or placental weights.

mouse

When female mice were given 0.3% dietary DEHP (450 mg/kg) for 7 days, prior to mating with untreated males, no litters were produced. A no-effect level of 0.01 % was identified in a part of the study where both males and females were treated.

(As might be appreciated from the sub-chronic toxicity section - effects on the testes, DEHP reduces the fertility of treated male rats).

c. Carcinogenicity

i) species: rat (Fischer 344), 50 of each sex per dose group dose level/dose period: 0, 6,000 or 12,000 ppm dietary, for 2 years

non-neoplastic findings: a high incidence of testicular atrophy in treated males given the highest dietary level (2%, 5% and 90% for the 0, 6,000 or 12,000 ppm groups respectively).

neoplastic findings: Increased incidences of hepatocellular carcinoma and neoplastic nodules were seen in male and female rats (Table 1).

There was a reduction in the incidence of interstitial cell tumours of the tests accompanying the testicular atrophy in males, given the highest dietary level (11/43; 23% compared with 47/49; 96%, in control males).

ii. species: mouse ($B6C3F_1$), 50 of each sex per dose group

dose level/dose period: 0, 3,000 and 6,000 ppm dietary, for 2 years

non-neoplastic findings: increased incidence of testicular atrophy in males (2%, 4% and 14% for the 0, 3,000 or 6,000 ppm groups respectively); increased incidence of chronic inflammation of the kidney in males (2%, 4% and 20% for the 0, 3,000 or 6,000 ppm groups).

neoplastic findings: increased incidence of hepatocellular carcinoma and adenoma in male and female mice (Table 2) with an increased incidence of metastatic spread to the lungs (Table 3).

d. Genotoxicity

DEHP has been tested in a variety of test systems including those designed to detect point mutations in bacteria, and in mammalian cells in vitro and in vivo, for chromosome effects in vitro and in vivo, for sister chromatid exchange, the ability to induce micronuclei in vivo, for unscheduled DNA synthesis and for the ability to induce dominant lethal effects in mice. Generally, negative results were obtained.

e. Effects in humans

i. general toxicity

DEHP has low acute oral toxicity in humans and is not irritant to the skin or eyes. It does not appear to be a potent skin sensi tizer.

ii) long term effects

A morbidity study in Germany of workers exposed to DEHP revealed no excess incidence of any disease. In the USSR and Italy industrial exposure to a number of phthalates was associated with a polyneuropathy but this may have been associated with exposure to the precursor alcohols.

In mortality studies, only the "healthy worker effect" was demonstrated in 221 workers at a plant producing DEHP in Germany. A case-control study of workers at a plant producing phthalates in the USA revealed no assoication between exposure and deaths from several types of cancer, but failure to specify the particular phthalates involved and the exposure levels encountered prevents any conclusions from being drawn from this study.

No chromosome abnormalities were noted in workers exposed to DEHP for periods of up to 30 years.

There is circumstantial - but no documented evidence to suggest that male patients exposed to DEHP during regular dialysis have an elevated incidence of testicular atrophy over unexposed individuals.

5. Evaluation

In modern production plants using sealed vessels, exposure to DEHP is probably low. The current Occupational Exposure Limit in the United Kingdom is 5 mg/m^3. DEHP is not used to any great extent in food contact materials in the UK and the intake is estimated to be 0.02 mg/person/day. Exposure can occur through medical procedures involving the use of plastics containing DEHP (e.g. blood transfusions, dialysis) and up to 3 mg/kg may be given in this way. Humans are also constantly exposed to DEHP in the environment where it is a widespread contaminant occurring in fresh and salt water, in the air and in food producing animals and plants. It is even found in the atmospheres of new cars and space craft where it arises from volatilisation from plastic materials.

The major concern from the intake of DEHP arises from the results of the carcinogenicity bioassays where liver cancers were produced in rats and mice. DEHP is not genotoxic and the liver cancers are throught to arise secondary to the hepatic peroxisome proliferation discussed earlier. The mechanisms is as yet unclear, but it may involve the peroxisomal generation of hydrogen peroxide in such large quantities from the oxidation of fatty acids, that it outstrips the ability of peroxisomal catalase to detoxify it. The excess hydrogen peroxide can then go on the generate active species which can then cause DNA damage, either directly or through the intermediary of lipid peroxidation. A range of compounds has now been indentified that share several properties with DEHP:

lack of genotoxicity

hypolipidaemic properties

induction of peroxisome proliferation

induction of hepatic tumours

A list of these is shown in Table 4.

It is not known if human liver can undergo peroxisome proliferation but experiments using human hepatocytes in vitro with certain peroxisome proliferating carcinogens suggest that it may not. Studies of humans given hypolipidaemic peroxisome proliferating drugs like clofibrate indicate that peroxisome proliferation may not occur in humans in vivo, at least at therapeutic doses. The proximate peroxisome prolierators in the rat (i.e.) the metabolites which induce the phenomenon, namely MEHP and its 5-keto/hydroxy derivatives are known to be formed in humans. However, the minimal dose for the induction of peroxisome proliferation in rats is around 10-50 mg/kg DEHP per day providing a large safety factor (32500 - 162500) over the estimated daily intake of 0.02 mg/person/day (approximately 0.00031 mg/kg/day). There is an approximately 100,000 fold safety margin for the effects of DEHP on reproduction toxicity over the likely human intake. Similarly there is a large safety margin for the effects on the testes but this may be reduced when the possible maximum dose is received during medical procedures. However, it is still likely to be sufficient to prevent toxic damage and in any case, must be viewed in terms of the benefits of the treatment.

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Table 1

Incidences of neoplastic nodules and hepatocellular carcinoma in rats given dietary DEHP for 2 years.

	control		low level		high level	
	male	female	male	female	male	female
neoplastic nodules	2/50 (4%)	0/50	5/49 (10%)	4/49 (8%)	7/49 (14%)	5/50 (10%)
carcinoma	1/50 (2%)	0/50	1/49 (2%)	2/49 (4%)	5/49 (10%)	8/50 (16%)
combined incidence	3/50 (6%)	0/50	6/49 (12%)	6/49 (12%)	12/49 (25%)	13/50 (26%)
combined incidence for males + females	3/100 (3%)		12/98 (12%)		25/99 (25%)	

Table 2

Incidences of hepatocellular carcinoma and adenoma in mice given dietary DEHP for 2 years.

	control		low level		high level	
	male	female	male	female	male	female
carcinoma	9/50(18%)	0/50	14/48(29%)	7/50(14%)	19/50(38%)	17/50(34%)
adenoma	6/50(12%)	1/50(2%)	11/48(23%)	5/50(10%)	10/50(20%	1/50(2%)
males + females						
carcinoma	9/100(9%)		21/98(21%)		36/100(36%)	
adenoma	7/100(7%)		16/98(16%)		11/100(11%)	

Table 3

Metastatic hepatocellular carcinoma in lungs of mice.

	control	low level	high level
males	0/50	7/49 (14%)	5/50 (10%)
females	0/50	1/50 (2%)	7/50 (14%)

Table 4

Peroxisome - proliferators shown to be hepatocarcinogenic in rodent species.

compound	species	reference
di(2-ethylhexyl)adipate	$B6C3F_1$ mouse*	11,12
gemfibrozil	CD rat**	13-15
tibric acid	male F344 rat	16
methapyrilene	F344 rat	17-19
clofibrate	F344 rat	20, 21
Wy-14, 643	F344 rat	22, 23, 29
fenofibrate	Sprague-Dawley rat	24
BR 931 (pyrinixil)	female acatalasemic (CS^b) mouse F344 rat	16
nafenopin	$CS^{(b)}$ mouse F344 rat	25, 26
methyl clofenapate	F344 rat	27
ciprofibrate	rodent species	28

* not in F344 rats, ** not in female F344 rats, not in CD-1 mice

LIVERPOOL 10:1 JOHAN

The value of human life depend on how worthwhile we used all of this life.

- more dangerous job - more worthwhile life.

Cost < benefit

Cost = benefit

10 : 1

Johan

Johan

Johan Sohaili

Ahmad Engman.

— A.D. Dayan

Carcinogenicity Testing

1. Once only 'experiment' — time — can animals
2. Mutagenicity testing — indicate genotoxic compounds — react with DNA.
   not-genotoxic compounds — being carcinogic.
3. Biological significance Versus statistical significance (weight of evidence). — 20-25% related to environment. (factor of life style).
4. What do you do with the results.
   action — positive (prudent) } — how it's agreed that should
   no action or wait
   ↓ result not very clear. (uncertainty).

Phthalates Case Study

1. Is there a carcinogenic hazard to man?
2. Is there a carcinogenic risk to man?
   If yes: what should be done about it?
   → how you regulate?

Prof. C Rossiter.

Recommended reading:
Stan Gore & DG Altman (1982) Statistics in Practice British Medical Assoc.

UK DHSS/IPCS Risk Assessment Seminar

Epidemiology Session - 4 December 1987

Man-made mineral fibres

Asbestos, particularly crocidolite and amosite, is recognised as a major occupational hazard and is also considered to be a public health hazard. Much interest has centred on the development, and safety, of alternatives to asbestos for fire and heat protection, for friction materials and for strengthening some cement products.

Man-made mineral fibres (MMMF) are increasingly being used as the primary substitute for asbestos, particularly for insulation purposes.

The primary critical properties of fibres which govern their hazard to man are:

Property		More hazardous state
diameter	-	finer
length	-	longer
solubility in lung	-	less soluble
brittleness	-	less brittle
rigidity	-	more rigid
curliness	-	straighter
surface activity	-	more active

The term man-made mineral fibres covers a range of different products dependent on the raw materials from which the fibres are made and on the method of manufacture.

The raw materials include glass, rock, slag (waste from some industrial production) and ceramics. If the manufacturing process involves **blowing** or **spinning** fibrous material from the melt, the product consists of disordered fibres of very variable length and diameter. These **wools** can contain a high proportion, by number, of respirable fibres.

Alternatively, fibres can be **drawn** from molten glass to form **continuous filament** fibres. The diameter of these fibres can be controlled more effectively so that fewer are in the respirable size range.

Some very fine glass fibres are manufactured for special purposes such as aircraft insulation and high quality filter papers. Most of these fibres are respirable, but these account for less than 1% of total production.

Ceramic fibres also form a small proportion of total production, being used for high temperature insulation. The term includes a high range of fibres, some of which are fine, rigid and durable.

Three background papers are attached:

The Epidemiology of Asbestos Related Disease
The Current Asbestos Standards
Man-Made Mineral Fibres: Quantifying Hazards

CER/SLB

25 November 1987

Medicine consists of:

1. Comparing 2 sets of results
2. Comparing one observation with previous results.

Without some knowledge of statistics, it's difficult to see whether the diff. could have arisen by chance or whether it is real.

Definition:

Statistics is science of dealing with variation so as to obtain reliable results.

Methods for:

- Estimating size of effects of interest (on the basis of partial information).
- Judging when effects are too large to have arisen just by chance (on the basis of partial information).

} range of uncertainty.

Determining which and how much partial information is worth seeking.

What causes variation?

Who? — observer ... & diff. definition
What? — experimental material, patients, samples, ...
Where? — animal cages, hospital beds, sites of injection ...
When? — time of day ...
How? — techniques, instruments, ...
Why? — purpose of study ...

THE EPIDEMIOLOGY OF ASBESTOS RELATED DISEASE

Asbestos, the inconsumable mineral described by Plutarch, used as a wick for the lamps of the vestal virgins, occurs in serpentine as the commonly used chrysotile, and in amphibole mineral rock in the form of crocidolite, amosite, anthophyllite, actinolite and tremolite, the latter three having little if any commercial value. The principal disorders related to asbestos exposure include pleural plaque formation, diffuse pleural thickening, diffuse interstitial pulmonary fibrosis termed asbestosis, lung cancer, and mesothelioma of the pleura or peritoneum. Less commonly, and only after very high past exposure asbestos appears to have been responsible for some cases of cancer of the larynx, ovary, stomach and perhaps for non Hodgkin's lymphoma of the gastrointestinal tract. Asbestos fibres embedded in the skin give rise to skin corns.

The occurrence of the principal disorders related to asbestos exposure will be considered. Asbestos has been used in industry only since about 1890. The first case of asbestosis was described in 1907, although not reported as such. An unequivocal relationship between asbestos exposure and pulmonary fibrosis was not established until 1928 to 1930 in Britain following which many cases were reported from Germany and elsewhere, and the first steps were taken to protect workers from exposure. An association between asbestos exposure and carcinoma of the lung was first suspected in the 1930s and epidemiological confirmation of this relationship was shown unequivocally by Doll (1955) who found a tenfold increased risk of lung cancer in asbestos workers with more than 20 years' exposure. The first case of mesothelioma of the pleura in an asbestos worker was reported in 1946, but it was Wagner et al (1960) who proposed a causal association from their observations on

Based on partial information, the estimate of a effect will only approximate 'truth'.

Based on different partial information, the estimate.

The confidence interval for an estimate describes how accurate and repeatable the estimate is —

Very accurate = small confidence interval → (135, 136)
Poor accuracy = wide confidence interval → (70, 215)

eg SMAP = 130

But - a confidence interval will not always include the true value.

- just because the occasional aberrant set of observation will occur.

Somehow, allowance for this phenomenon must be made.

- and the usual working idea is to choose the size of the confidence interval so that it includes the true value usually
  - ie 95% correct
  5% wrong.

Statistical significance

Caution:

1. Statistical significant ≠ Reliable.
   - State decision level.
2. Statistical significance = evidence ≠ proof
3. Non-significance ≠ evidence
   ≠ proof.
   - of no difference.
5. Significance gives NO information nature of association. NOT proof of causation.
6. Statistical significance ≠ practical significance.

crocidolite miners in South Africa. In the asbestos hills West of Kimberley there was heavy environmental pollution in the small townships clustering round the mine workings and mesothelioma was observed both in workers and in the local communities. Cases were reported subsequently with increasing frequency from Britain, USA and other countries following exposure in factories, shipyards and in the community. In Britain, regulations for the surveillance of workers engaged on the manufacture of asbestos products were introduced in 1933, and surveillance, which included periodic chest x-rays, was extended to include insulation workers and other users of asbestos in 1969. The progressive revision of exposure limits for asbestos will be described following consideration of dose-response relationships. By 1960, the need for information on the occurrence of diseases related to asbestos, and their relationship to exposure levels was evident, and many studies followed, in particular in Britain and in the USA.

Problems in establishing a dose-response relationship

The attempt to establish dose-response relationships for asbestos exposure is beset with many problems. Amongst these should be included the long latent interval between initial exposure and evidence of an adverse effect, the features of which may be difficult to define; the unreliability of diagnosis leading to inexact certification; exposure to more than one type of asbestos each of which may have a different potential for producing an adverse effect; the inadequacy or even absence of data on past exposure; the, until recently, crude methods in use for dust sampling and fibre identification and counting, and the confounding effects of cigarette smoking.

Conclusion

1. Statistical methods are tools:

- to provide estimation of the size, and precision of an experimental or observational diff.
- to aid in evaluation of or interpretation of an experimental or observational diff.
- to provide guidance on what (and how much) information should be collected to answer research questions.

While these problems are still with us, precision in epidemiological studies has been improved with the development of standardised questionnaires on respiratory symptoms; the use of the ILO classification of chest radiographs, extended to include irregular opacities and pleural abnormalities; the use of panels of assessors for reading the chest x-rays; the standardisation of respiratory function tests; and, in particular, the measurement of transfer factor, and the quantitative method for assessing finger clubbing. With regard to exposure assessment, dust sampling methods have been greatly improved; the early practice of recording total particle counts has given way to fibre counting and this has become more precise with improvements in microscopy; the use of the eye piece graticule; phase contrast illumination; membrane filters and the introduction of transmission and scanning electron microscopy for fibre identification. Fibre counts in lung tissue have been improved by digesting tissue with potassium hydroxide instead of by ashing. However, difficulties arise in attempting to equate figures for dust concentrations obtained at different times, recorded in earlier days in terms of millions of particles per cubic foot, and now in terms of fibres per millilitre.

Benign pleural abnormalities

Pleural plaques, raised areas of hyaline tissue which may calcify with the passage of time, are present in up to about 40% of persons with regular occupational or environmental exposure to asbestos, but their presence is likely to be underestimated as they may be missed on standard chest films, although readily identifiable on CAT scanning. In a sample of dockyard workers with asbestos exposure, the risk amongst those with pleural plaques subsequently developing asbestosis was increased compared with those without

such plaques (McMillan and Rossiter, 1982). However, other factors contribute to the formation of pleural plaques and while their presence in those exposed to asbestos may be taken as a warning sign, the association with asbestosis is weak. Plaques are also seen in those with environmental exposure to anthophyllite, tremolite and zeolite although asbestosis is a rare sequel. In those occupationally exposed, the proportion of those affected is related more closely to time since first exposure than to intensity of exposure to asbestos dust. Pleural plaque formation cannot be used for the purpose of establishing dose-response relationships. A high prevalence of pleural calcification has been observed in a rural area in North-West Greece, but there is no evidence of an association with previous exposure to asbestos (Bazas et al, 1985).

Asbestosis

The diagnosis of asbestosis is made on a history of exposure together with the clinical, physiological and radiographic features of the disorder. Exposure should have entailed the handling of asbestos products for a minimum period of two years, unless this was exceptionally heavy, and initial exposure to have occurred at least ten years previously. Shorter periods, and the absence of asbestos bodies in sputum or on bronchopulmonary lavage are against a diagnosis of asbestosis. Diagnosis can be made with a high degree of accuracy in advanced cases of the disease, but is uncertain and difficult in the early stages. In mortality studies the frequency of asbestosis is likely to be underestimated, giving rise to error in risk estimation, in particular at lower levels of exposure. In heavily exposed workers, asbestosis mortality is related to intensity of exposure and time since first exposure, and is higher in cigarette smokers. Smokers of more than four cigarettes daily have been estimated to be at a greater risk of developing asbestosis than non-

smokers (Rossiter and Berry, 1978). The risk of developing asbestosis appears to be greater in the textile industry than in mining and milling, or in the manufacture of friction products (McDonald, 1984). While WHO (1986) concluded that there is no substantial evidence that asbestos fibre type influences the frequency or severity of pulmonary fibrosis, fibre counts for crocidolite have invariably been found to be higher in fibrotic lung tissue than fibre counts for chrysotile. Amphiboles are in general retained longer in lung tissue than chrysotile, which is subject to fragmentation and more effective clearance of its shorter fibres. Cigarette smoke reduces long term deep lung clearance and retention may explain the greater frequency of asbestosis in cigarette smokers.

With regard to dose-response relationships, taking the presence of basal crepitations as a criterion for asbestosis, in a study by Acheson and Gardner (1979), the annual incidence in men with cumulative doses below 100 fibres/ml years was of the order of 2%. The incidence of asbestosis in asbestos exposed workers in industrialised countries is at the present time declining. In asbestos workers initially employed after 1971 to fibre counts meeting current standards in Britain, a low prevalence of detectable x-ray changes was reported (Jacobson et al, 1984). There is no evidence to suggest that general environmental or neighbourhood exposure results in an increased risk of asbestosis.

Lung cancer

Bronchial carcinoma and mesothelioma are now the principal asbestos related health hazards, and both are increasing in incidence in most industrialised countries, as a result of past heavy exposure. Bronchial

carcinoma is more often squamous, but may be adenocarcinomatous or less often oat cell in type. The increased risk from bronchial carcinoma in asbestos workers is first evident 12 to 30 years after initial exposure, rising with length of exposure. There is a clear relationship with smoking, bronchial carcinoma being far commoner in smokers and ex-smokers with occupational asbestos exposure than in non-smokers. Smoking introduces a major confounding factor leading to uncertainty in risk assessment, because of the lack of accurate information in most studies. A review of available studies at the time (Saracci 1981) concluded that the joint effect of asbestos exposure and cigarette smoking was more than additive but not always multiplicative. More recent data support the multiplicative model, in particular for the amphiboles.

Fibre type, size and amount, or intensity of exposure, have to be considered in risk assessment. Exposure to chrysotile, crocidolite and amosite have all been shown to give rise to increased risk of bronchial cancer, but their relative potency is unclear. This is in part because in many workplaces mixed exposures occur. However, in Britain, in women employed in gas mask manufacture during the war, those exposed to crocidolite had a greater excess of lung cancer than those exposed to chrysotile alone (McDonald and McDonald, 1978). The observations made above on fibre size with regard to retention in the lung and fibrogenic potential, are likely to apply equally to bronchial carcinoma. Crocidolite fibres are far more numerous in lung tissue than chrysotile fibres in bronchial carcinoma. Retention time in the lung, fibre length and diameter may be relevant variables.

Mathematical models have been derived from incidence data at high occupational exposure levels in an attempt to estimate risk at low levels of

exposure. A linear model relating bronchial cancer incidence with dose in terms of both concentration and time is valid at the higher levels. Such a model assures that the relative risk is increased in approximate proportion to both intensity in terms of fibres/ml and duration of exposure.

WHO (1986) quote the formula:

$$I_A\ (d,f,a,s) = I_U\ (a,s)\ x\ (I + K_L \cdot d \cdot f)$$

where the left side of the equation denotes lung cancer incidence among asbestos workers aged 'a' who smoke 's' cigarettes per day and have been exposed for a total duration of 'd' years at an average level of 'f' fibres/ml. I_U denotes lung cancer incidence at the same age in an unexposed population with similar smoking habits. K_L is a constant characteristic of the mineral type and distribution of fibre dimensions of the asbestos. The relative risk, which equals $I + K_L \cdot d \cdot f$, is thus increased in proportion to $d \cdot f$, years of exposure at an average level of 'f' fibres/ml, i.e. the cumulative dose (fibre/ml years). The WHO report stresses the uncertainties inherent in this formula, with regard to historical concentration measurements, fibre size distributions associated with a given fibre level, variations in the activity of different fibre types and inadequate information on smoking habits. Any assessment of risk at low levels of exposure, in particular at levels which may be encountered in the general environment, which are orders of magnitude below levels of exposure in the populations from which the estimates were derived, must reflect the above uncertainties.

Mesothelioma

The incidence of mesothelioma has risen rapidly over the past 30 or so years, with about 500 new cases per year now being reported from England and Wales. Some 85% of these are related to asbestos exposure, the rest being of unknown origin. Cases have occurred most often in crocidolite miners in South Africa and Western Australia, in limpet sprayers, insulation workers and dockyard workers, in persons living in the vicinity of crocidolite asbestos mines in South Africa, and a few cases have occurred in women handling asbestos contaminated clothing. Cases occurred in women filling gasmask canisters with crocidolite during the second world war, but not when using chrysotile (Acheson et al, 1982). Very few cases of mesothelioma have been reported following chrysotile exposure. In addition to crocidolite, mesothelioma has followed exposure to other amphiboles, in particular amosite. In a recent study in a chrysotile mining area in Cyprus, several cases of mesothelioma were diagnosed, both among asbestos miners and in the local villages where tremolite was identified as a contaminant in the environment and was found to be present in lung tissue (McConnochie et al, 1987). A number of well conducted studies have shown a clear relationship between crocidolite exposure and an increased incidence of mesothelioma. In contrast to bronchial carcinoma, cigarette smoking does not appear to increase the risk (McDonald, 1984). There is a long latent interval of some 20 to 40 years from initial exposure before mesothelioma becomes clinically apparent. In general, although the effective dose required for mesothelioma is less than that causing asbestosis or lung cancer, most cases have followed work in conditions of heavy exposure for at least two years (Newhouse et al, 1976). Most cases of mesothelioma contain at least 10 million asbestos fibres in their lungs.

Risk assessment based on a mathematical model to link fibre exposure with incidence of mesothelioma is at the best tenuous. In contrast to the linear relationship with cumulative dose proposed for lung cancer, an exponential relationship with time since first exposure appears to be more appropriate for mesothelioma. WHO (1986) cite a model proposed by Peto et al (1982) in which the predicted incidence rate I, t years after first exposure, is proportional to $t^4 - (t - d)^4$, where t denotes years after first exposure and d is duration of exposure.

Thus: $$I\ (t,f,d) = K_M \cdot f \cdot (t^4 - (t - d)^4)$$

where f is the level of exposure in fibres/ml. The constant K_M depends on the type of fibre and the distribution of fibre dimensions. As with the lung cancer model, there are reservations with the mesothelioma model. The K_M value has been generated from amphibole and mixed fibre data and cannot be used for chrysotile. The WHO Task Group concluded that any number in terms of cases of mesothelioma per million people will carry a variation over orders of magnitude.

Exposure limits

Further observations at the asbestos processing plant in Britain where the relationship with bronchial carcinoma was first recognised, led to an exposure limit for the prevention of asbestosis of 2 chrysotile fibres/ml as a UK Hygiene Standard, in 1969. It was subsequently found that workers there had been exposed to crocidolite as well as chrysotile. Nevertheless, the improvement in environmental conditions which dated back to 1933, led to a

fall in lung cancer risk compared with the general population from 10:1 to 1.16:1 (Peto et al, 1977). Since 1969, with the accumulation of new evidence obtained from epidemiological studies, the UK Hygiene Standard has been progressively reduced. Crocidolite, which had been much used previously, in particular for the lagging of ships' boilers, was no longer imported into Britain after 1970, and the exposure limit reduced to 0.2 fibre/ml. In 1983, a new Hygiene Standard was introduced of 1 fibre/ml for chrysotile, 0.5 fibre/ml for amosite, and 0.2 fibre/ml for crocidolite. The use of amosite was banned a year later, when exposure was again reduced to the present Hygiene Standard of 0.5 fibre/ml for chrysotile and 0.2 fibre/ml for both crocidolite and amosite. Similar standards have been introduced by the USA, and have been recommended by the ILO.

It is considered that, with present epidemiological methods the current exposure limits should reduce the risk of asbestos related disease to barely detectable levels. However, in the not too distant past asbestos counts were frequently in the range of 5 to 15 fibres/ml and counts of 50 fibres/ml were not exceptional. Due to the long latent interval for bronchial carcinoma and for mesothelioma, the mortality from these conditions has continued to rise. The highest exposures, which caused asbestosis, were however curtailed in the late 1960s when realistic hygiene standards were first introduced. The effect of these measures is already being seen by a change from increase to relative constancy in the annual mortality from asbestosis, and the reversal in the upward trend in Britain in the prevalence of early radiographic abnormality in persons first exposed since 1971, compared with those of similar age and smoking habit who were exposed previously.

UK Control Limits for Asbestos

Asbestos type	1973	1983	1984
Chrysotile	2	1	0.5
Amosite	2	0.5	0.2
Crocidolite	0.2	0.2	0.2

Postulated Models for Effects of Asbestos Exposure on Incidence of Lung Cancer and Mesothelioma

(1) **Postulated Model for Lung Cancer Incidence**

$$I_A\ (d,f,a,s) = I_U\ (a,s) \times (I + K_L \cdot d \cdot f)$$

I_A - bronchial cancer incidence among asbestos workers aged 'a', who smoke 's' cigarettes/day, exposed for 'd' years at an average level of 'f' fibres/ml

I_U - lung cancer incidence at same age 'a' in unexposed populations with similar smoking habits

K_L - a constant, characteristic of mineral type and distribution of fibre dimensions

(2) **Postulated Model for Mesothelioma Incidence**

$$I\ (t,f,d) = K_M \cdot f \cdot (t^4 - (t - d)^4)$$

t - years since first exposure

f - level of exposure (fibres/ml)

d - duration of exposure in years

K_M - constant, characteristic of mineral type and distribution of fibre dimensions

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THE CURRENT ASBESTOS STANDARDS

Asbestos causes disability, disease and death – certainly from asbestosis, lung cancer and mesothelioma and perhaps from other cancers and chest disease. In order to set a standard based on scientific evidence, quantitative assessments of the burden of dust imposed on workers have to be made; these assessments of "dose" must then be related to the associated risks of health effects. The dose-response relationship must be determined.

The results of scientific investigation may provide the stimulus for occupational hygiene standards being demanded and agreed. But in practice the standards which are agreed are the outcome of political argument and political compromise. Scientifically ascertained facts may identify and to some extent quantify risks but they cannot settle all argument. This may be inevitable where people's health and even their lives are involved; but political compromise is inevitable also because the ascertained facts are rarely entirely reliable.

This is so even in the case of asbestos which is probably the most extensively studied hazardous material. It is apparent from a study of the data on exposure levels and disease incidence from which the current asbestos standards are derived.

DOSE-RESPONSE METHODOLOGY

Ideally the shape of the dose-response curve should be known and for this both dose and response have to be defined accurately in measurable and unambiguous terms: since epidemiology is essentially observational, the derivation of the relationship requires much complementary data on dose and response. Neither measurement is straightforward.

MEASUREMENT OF DOSE

Clearly the ideal measure of exposure is the biologically active dose, combining the amount inhaled with patterns of retention and elimination to determine the number of fibres which reach the target organ and the length of time that they remain active. All that we can do to estimate this, however, is to measure the airborne concentration as near as possible to the breathing zone, and we still do not know what properties of the fibres are relevant to specific health effects – is it length, or diameter, or mass, or surface area? Or instead should we count say the number of fibres of length greater than 8μm or of diameter less than 0.25μm? Or is it some other parameter or combination of parameters? Moreover the term asbestos includes a group of fibrous minerals (of which the more important industrially are chrysotile, amosite and crocidolite) – to what extent does the type of fibre affect the risk? And does the risk depend on the industry or on the job of the worker who is exposed? In assessing the ultimate risk of disease what weights should be given to exposures at different times in the past? And finally, to determine an individual's total exposure, airborne concentrations are needed throughout the period of many years when he or she has worked with asbestos: are measurements taken at different times comparable, even after conversion factors have been applied between different methods of measurement?

Table 1 shows the history of sampling methods for asbestos since 1951 (before then virtually the only "measurements" were based on visual assessment of "dustiness"). The dates of the changes from one method to another will however have varied to some extent between companies.

TABLE 1: SAMPLING METHODS FOR ASBESTOS USED IN THE UK SINCE 1951

1951-61	Casella thermal precipitator (sampling for limited periods only, about 10 minutes). (In the US the midget impinger was used for many years.)
1961-64	Long-running thermal precipitator (continuous sampling throughout a shift).
1964-74	Membrane filter, static sampler.
1974 to present	Membrane filter, personal sampler.
1979 to present	Membrane filter (personal), sample assessed by using an eye-piece graticule.

The midget impinger used in North America operates on a principle totally different from those on which the thermal precipitator and membrane filter depend, and work has only just been published relating the midget impinger to the membrane filter (Parsons et al 1986). It was concluded that conversion ratios from particles to fibres subsumed too much variation to allow use of a single value. Arbitrarily a ratio of 3:1 is often used to convert thermal precipitator counts of asbestos particles (in millions of particles per cubic foot) to the present standard of fibres per millilitre by membrane filter with graticule. But Acheson and Gardner (1980) state that the conversion "at best introduced additional uncertainties and was at worst indefensible", and Harries (1971) found no

TABLE 2: DIAGNOSIS OF ASBESTOSIS

		Diagnosed *post mortem*		
		Yes	No	Total
Diagnosed before death	Yes	5	3	8
	No	3	16	19
	Total	8	19	27

TABLE 3: FIBRE TYPES REPORTED AS HAVING BEEN USED IN ROCHDALE PLANT

Date of report	*Authors*	*Fibres reported as being used*
1955	Doll	All chrysotile
1978	Peto	"A little" crocidolite
1979	Hardie	2500 tonnes crocidolite during 1931-1970
1983	Acheson & Gardner	10,000 tonnes crocidolite during 1931-1970
1985	Peto & Doll	10,322 tonnes crocidolite during 1932-1968, constituting 2½% of total fibre and 5% of total used in textile manufacture

TABLE 4: FIBRE CONCENTRATIONS IN THE ROCHDALE PLANT, 1933-1971, AS REPORTED BY DIFFERENT AUTHORS

	Period to which measurements refer					
	1933-1950	1951	1956	1961	1966	1971
	Method of measurement					
Authors cited	No measurements	Area samples, thermal precipitator (TP)			Membrane filter or Royco automatic particle counter	
		Normal TP		Long-running TP		
Peto, Doll et al (1977)	—	10.8	5.3	5.2	5.4	3.4
Peto (1980)	—	32.4	23.9	12.2	12.7	4.7
Peto, Doll et al (1985)	—	4.5-28.0	4.4-28.0	2.5-20.0	2.5-20.0	2.7-7.5

All concentrations in fibres/ml.

TABLE 5: STUDIES OF MORTALITY OF ROCHDALE ASBESTOS WORKERS FROM VARIOUS REPORTS

Authors	Study group	No in group studied	Total deaths		Deaths from:		
					Lung cancer		Mesothelioma
			Obs.	SMR	Obs.	SMR	Obs.
Doll (1955)	Employed before 1933	113	39	253	11	1375	—
Peto (1980)	First employed 1933-62	679	239	113	40	172	7
Peto, Doll et al (1985)	First employed 1933-74	3211	1113	114	132	131	11

No SMR is given for mesothelioma because it is a rare cause of death among people not exposed to asbestos (1/10,000).

consistent correlation between results from a long-running thermal precipitator and a membrane filter sampler working side by side. Indeed in one trial the correlation was negative. It must also be noted that the changes in the use of membrane filters, ending up with assessment using the eye-piece graticule, in effect made the asbestos standard five times more stringent since dust concentrations recorded as 1 fibre/ml in 1965 (static sampling) would now be assessed as about 5 fibres/ml (sampling by personal sampler). Thus even when dust measurements are available for many years past, the dose that each worker received remains in considerable doubt, even without taking retention and elimination into account.

ASSESSMENT OF RESPONSE

Assessment of response is no more clear-cut. Responses may be either fibre-specific (ie asbestosis and mesothelioma) or non-specific (lung cancer, other cancers, respiratory disease, etc). Clearly the non-specific can never be attributed unequivocally to asbestos: taking lung cancer as an example, even among non-smokers there must be some uncertainty, and the high incidence of both lung cancer and other respiratory diseases in this country means that any excess due to asbestos will be over and above a high, and continually changing, background level (and in any case its interpretation will be complicated by the fact that Saracci (1977) has shown that smoking and lung cancer act synergistically in this context).

Perhaps surprisingly, however, even the fibre-specific diseases give rise to problems, in their case because there are no clear-cut criteria for diagnosis. Table 2 compares diagnoses of asbestosis in 27 workers before and after death (Berry 1981) and indicates that serious disagreements can occur between doctors highly experienced in this field.

Detailed studies of mesothelioma show that it too may be either under- or over-diagnosed. Consequently evidence of excess mortality comes from comparing observed mortality in an exposed group of workers with that expected on the basis of national or local death rates. However, as discussed later, the choice of a control group is critical and can bias the conclusion. Thus stronger evidence is provided by those studies which show an increasing excess mortality with increasing duration and/or intensity of exposure.

In the assessment of excess morbidity the choice of a suitable comparison group is even more difficult. Smokers in particular suffer from morning cough, breathlessness and bronchitis, any of which might be caused by exposure to asbestos. They also have impaired lung function and changes of X-ray appearance indistinguishable from those in early fibrosis. For all of these reasons the most convincing evidence of occupational risk is the epidemiological demonstration of excess morbidity and excess mortality among exposed groups of workers, which increase with increasing fibre dose.

SHAPE OF RELATION

A standard is essentially a means of predicting the outcome of future exposures and to derive this the data on dose and response must be brought together to form a dose-response relation – about which these data are the only source of information. To describe this relation an infinite variety of curves can be postulated and some general types are shown in fig. 1.

FIG. 1: POSSIBLE SHAPES OF THE DOSE-RESPONSE RELATIONSHIP

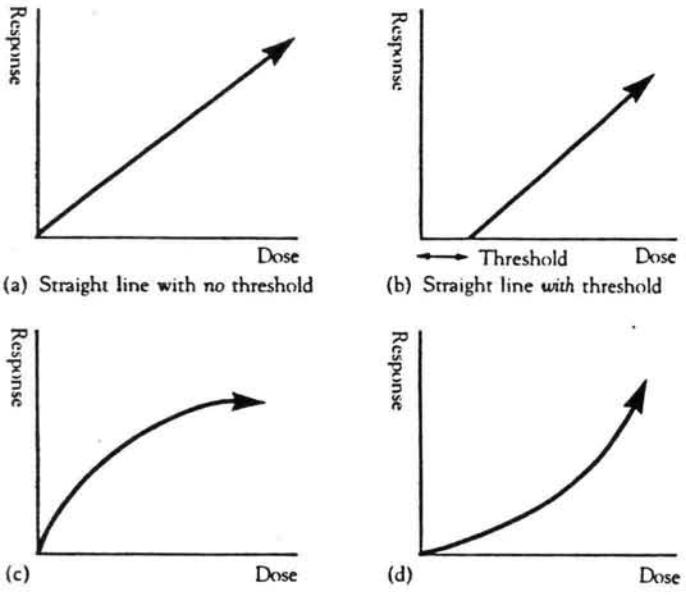
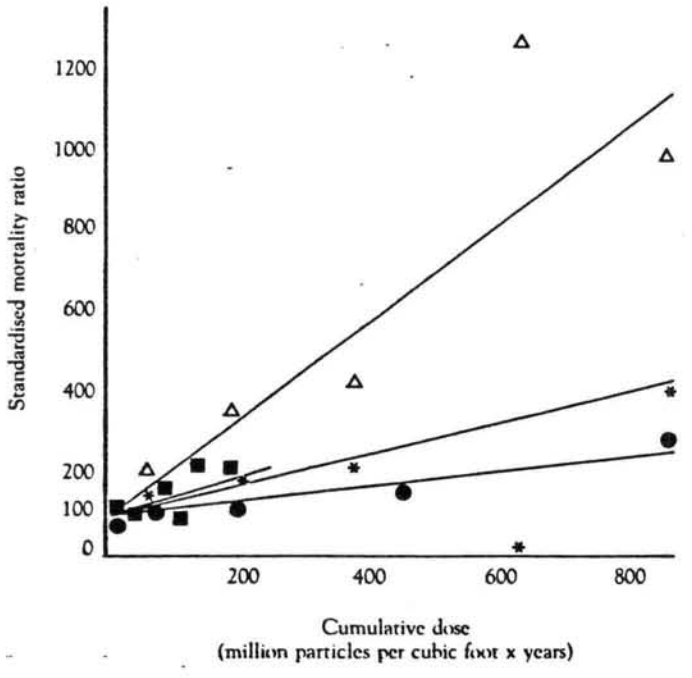


FIG. 2: DOSE-RESPONSE CURVES FOR LUNG CANCER IN NEW JERSEY ASBESTOS PRODUCTION AND MAINTENANCE WORKERS, QUEBEC MINERS AND MILLERS AND ROCHDALE WORKERS 20 OR MORE YEARS AFTER FIRST EMPLOYMENT



Freehand lines have been drawn.
△ Maintenance-service workers; * production workers;
• Quebec miners and mill workers; ■ Rochdale workers, first employed 1933 or later.

Data from Peto, J et al (1985) (Rochdale workers)
Data from Acheson, E D and Gardner, M J (1980) (other studies)

There is no *a priori* reason for expecting the relation to have any particular form, and therefore applying the principle of "Ockham's razor" that one should choose the simplest possible explanation until it can be shown to be inadequate, the first model is a straight line with no threshold ((a) in fig. 1); should this prove inadequate the second hypothesis would be a straight line relation with a threshold ((b) in fig. 1), the basis of the choice being once again not the certainty of the model being right but its simplicity and the absence of contrary evidence. (It was just in this way that Newton chose to state his laws of motion in the simple way that he did: the observations available in the 17th century were not precise enough to reveal any discrepencies. By 1900 more accurate instruments had detected them, so that Newton's laws had to be replaced by Einstein's principle of relativity.)

As the data below indicate, for asbestos there is no evidence of pathological effects at the concentrations required by present regulations because all workers whose exposure has been measured over long periods have had much greater total dose. Also, since the data for higher doses are widely scattered it is not possible to derive a threshold by extrapolation back to low dose. This does not mean that there is no threshold, only that the data are not good enough to detect one. Similarly, the data are not good enough to differentiate between a straight line relationship and one with curvature.

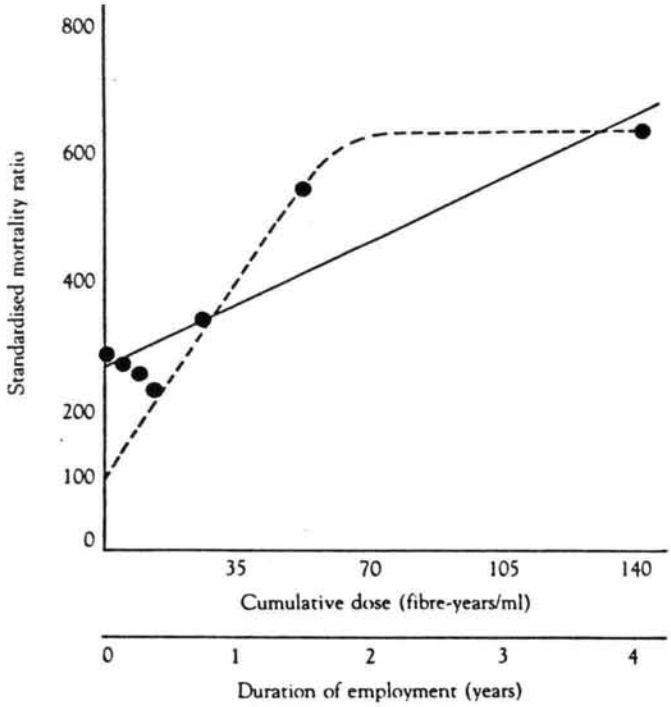
INCONSISTENCIES IN AVAILABLE DATA — THE ROCHDALE STUDIES

These are not the only problems, however, and the series of studies based on the Rochdale asbestos processing plant highlights the difficulties of deriving a relationship. The population was first studied in 1955 by Sir Richard Doll, and this study formed the basis of the British Occupational Hygiene Society's report in 1968 which led to the 2 fibres/ml UK standard. By 1968 it was generally accepted that some other types of asbestos, at that time notably crocidolite, were much more dangerous than the type used in greatest quantity, chrysotile (a difference which had not been appreciated at the time of the original 1955 study). Consequently the type of fibre that had been used in the plant was of crucial importance in the interpretation of the data. In 1955 this had been stated to be all chrysotile but, as table 3 shows, in subsequent reports it gradually emerged that this was far from being the case.

The reported fibre concentrations at Rochdale are similarly inconsistent (table 4). In this instance there are differences of interpretation of the same samples, even for samples collected as recently as 1971, and the epidemiological data although not all relating to the same periods show large differences between standardised mortality ratios between those derived by Doll in 1955 and in more recent figures (table 5). (Simply stated, the standardised mortality ratio or SMR is an index which is the ratio of the recorded mortality of the group of interest to the mortality of a reference population of the same ages and sex, expressed as a percentage: the specification of an appropriate reference population may however be both controversial and the determining factor in the statistical argument.)

No doubt the gradual fall in SMR is partly attributable to the fact that the latter estimates included many workers who

FIG. 3: MORTALITY FROM LUNG CANCER AMONG AMOSITE INSULATION PRODUCTION WORKERS ACCORDING TO ESTIMATED CUMULATIVE DOSE OF EXPOSURE TO ASBESTOS AND DURATION OF EMPLOYMENT



●● individual data points from Seidman et al (1979)
--- dose-response relationship from Nicholson (1981)
—— dose-response relationship from Liddell (1982)

From Acheson, E D and Gardner, M J (1983)

had been employed in the works only after conditions began to improve, but the changing conditions and the huge range of uncertainty in the estimates of airborne concentrations of fibres throw into relief the problem of establishing a dose-response relation.

INCONSISTENCIES IN AVAILABLE DATA — NORTH AMERICAN STUDIES

The data from North America add to the confusion. Fig. 2 shows straight line dose-response relationships ("response" being expressed by the SMR for lung cancer) fitted to data from asbestos workers doing two types of work in New Jersey, and for Quebec miners and mill-workers: the data from Rochdale are also presented. The four lines shown can be extrapolated back to SMR = 100 at zero dose, thus providing no evidence against the hypothesis that there is no threshold. The slopes are however quite different in each instance, and any standard derived will depend on the study chosen. But it should be noted that in any event the standards based on the American and Rochdale data need not be comparable because the sampling in the US was by midget impinger and (as mentioned above) the data derived could not be related simply to that based on use of the thermal precipitator in the UK at that time. An important feature of all firm lines is that they are based on studies in which the lowest cumulative dose group with an SMR definitely greater than 100 was equivalent to about 5 fibres/ml for 40 years. These results can tell us very little about the existence of a threshold or about the risk of death at the very low concentrations now set as standard.

Even greater problems arise in considering the lung cancer relations for amosite insulation workers (fig. 3) (Seidman et al, 1979) and the South Carolina textile workers (fig. 4) (Demont et al, 1982). The figures show the relations fitted by Liddell and Hanley (1985) and by Nicholson (1981). Liddell used straight lines without constraining them to an SMR of 100 for zero exposure, whereas Nicholson did impose this condition. The interpretations are very different with the Nicholson analysis suggesting that straight lines are not appropriate and Liddell predicting excess lung cancer mortality even in the absence of exposure. The latter is more likely to be "correct" as local death rates were not used to calculate expected mortality. In the Seidman et al study, causes of death were also investigated, and changed if incorrect, but expected numbers of deaths could not similarly be corrected, leading to a further bias in the SMRs.

It is no wonder that the National Academy of Sciences Risk Assessment Committee (1953) said that "The dominant analytical difficulty is pervasive uncertainty".

MESOTHELIOMA

The discussion above relates to lung cancer. In the case of mesothelioma the association with crocidolite rather than chrysotile is rather more clear-cut (Acheson et al, 1982; table 6).

TABLE 6: MORTALITY AMONG WOMEN WHO HAD ENGAGED IN THE MANUFACTURE OF GAS MASKS CONTAINING CROCIDOLITE *OR* CHRYSOTILE

	Exposure to	
	Crocidolite	Chrysotile
No. of women	757	570
Total deaths	219	177
Lung cancer deaths	13	6
Mesothelioma deaths	5	1
SMR, lung cancer	209	124

Exposure mainly 1936-45; died 1951-1980.

CONCLUSION

Despite the conflicting data cited above it is still possible to summarise the points on which there is a general consensus of opinion:

(1) the risk of asbestosis is effectively nil at today's standards;

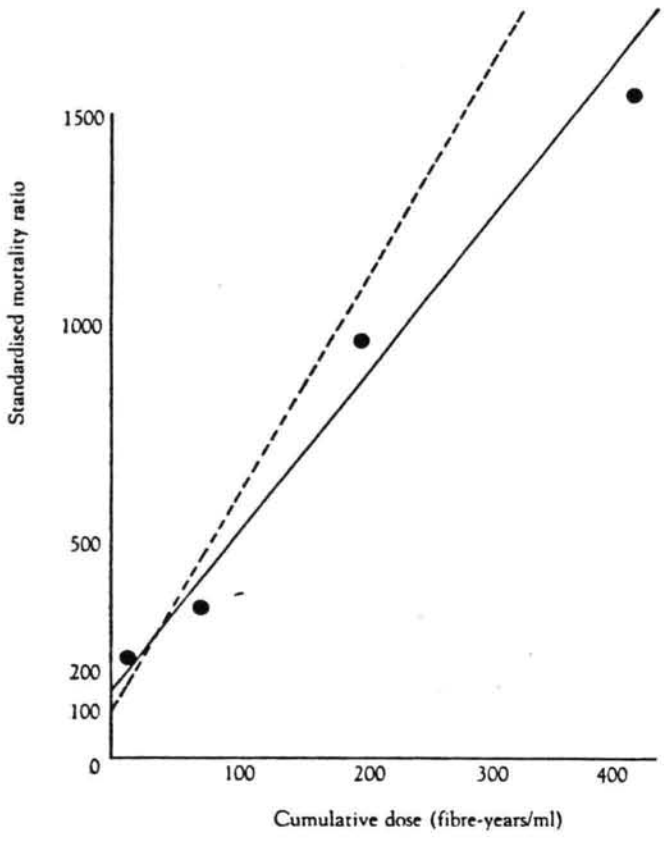
(2) the evidence in relation to gastro-intestinal cancers is not strong, but it appears to be more strongly associated with crocidolite and amosite;

and the following points from the excellent and comprehensive report of the Royal Commission in Ontario (1984):

(3) there is strong evidence that crocidolite and amosite fibres tend to be more hazardous than chrysotile fibres;

(4) "we cannot condone any manufacturing activity that involves the use of crocidolite or amosite";

FIG. 4: MORTALITY FROM LUNG CANCER AMONG CHRYSOTILE TEXTILE PRODUCTION WORKERS ACCORDING TO ESTIMATED CUMULATIVE DOSE OF EXPOSURE TO ASBESTOS



●● individual data points from Dement et al (1982)
--- dose-response relationship from Nicholson (1981)
—— dose-response relationship due to Liddell from McDonald et al (unpublished)

From Acheson, E D and Gardner, M J (1983)

(5) the risk associated with mining, milling and general manufacture can be kept within acceptable limits by adopting a standard of concentrations less than 1 fibre/ml;

(6) in textile manufacture the standard should be 0.04 fibres/ml;

(7) among workers who have handled only chrysotile, mesothelioma has rarely been recorded;

(8) among workers who have handled amphibole asbestos (which includes both crocidolite and amosite) there can be an appreciable mortality rate from mesothelioma;

(9) only amphiboles are associated with the causing of peritoneal mesothelioma.

To these comments it might be added that out of more than 100 cases of mesothelioma investigated not one was recorded to have less than 10,000,000 asbestos fibres in the lungs.

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MAN-MADE MINERAL FIBRES: QUANTIFYING HAZARDS

In 1972 two papers, by Stanton and Wrench and by Pott and Friedrichs, were published describing experiments in which man-made mineral fibres (MMMF) had been implanted intra-pleurally in rats. In both instances mesothelioma had resulted, and this was taken as implying that there might be a long-term health hazard to workers handling these fibres. It was therefore of crucial importance to the MMMF-producing industry to ascertain whether or not this hazard was real, and if so to assess how serious it was. Until then animal experiments had provided no evidence of MMMF inducing fibrosis, lung cancer or mesothelioma and there had been only very occasional and equivocal case reports of fibrosis in humans.

Subsequent animal inhalation experiments showed no evidence sufficient to cause much concern about human hazard. Nevertheless, the impact of the intra-pleural implantation studies led the trade associations of the MMMF-producing industry in the USA and in Western Europe to sponsor epidemiological and environmental research to assess the evidence of excess mortality and morbidity among MMMF production workers. The results of the mortality studies are discussed in this article.

PRODUCTION AND CHARACTERISTICS OF MMMF

MMMF have been made commercially for many years; Saracci *et al* (in the paper cited below) state that the plants that were the basis of their study started production between 1900 and 1955. The salient features of the production process may be classified simply as follows (reproduced from McDonald, 1984):

	Continuous filaments	*Wools*	*Fine fibres*
Made from	glass	glass, rock, slag	glass
Fibre diameter, μm	3.5-9.5	1.0-15.0	0.05-1.0
Uses	textiles, reinforcement	insulation	filters, papers etc

Rock or slag wool for insulation has an optical diameter of 4-6μm but much finer fibres are also produced.

EXPOSURE-RESPONSE METHODOLOGY

The general problems of deriving exposure-response relations for workers exposed to possibly harmful materials were discussed in an earlier article (OHR 1) in relation to the current asbestos standards. Naturally the same considerations apply to MMMF. Moreover since asbestos fibres and MMMF are similar in shape and to some extent in size many of the specific problems are similar also: the only practical measure of exposure is in both instances the concentration of airborne dust in the environment at the workplace, which is as near to the "biologically active dose" as we can get; and for MMMF, as for asbestos, methods of measurement have changed in the past and those for MMMF will probably soon change again with the introduction of a mass standard. As with asbestos, both fibre-specific and non-specific responses are concerned. Interest in the problem of MMMF started from the suggestion that there is a general response to mineral fibres; the hypothesis to be tested, therefore, is that MMMF is similar to asbestos in its effects on the lung. The existence of a fibre-specific pulmonary fibrosis (pneumoconiosis) analogous to asbestosis and attributable to MMMF has however yet to be proven (and pneumoconiosis can be caused by non-fibrous dusts, as for example by silica) and the other fibre-specific response to asbestos, mesothelioma, was found in only one worker in the extensive studies described below. The problem of quantifying the hazards associated with work with MMMF therefore reduces to that of estimating the increased mortality (and, if non-fatal diseases are identified, the morbidity also, but this is not discussed in this paper) from pulmonary diseases among workers and former workers in the industry.

STUDIES OF MORTALITY

There have been two major studies of mortality in the MMMF production industry, one in the USA and one in Europe. They were very similar in design: in each case the study covered several plants, identifying the workers who had worked in the industry many years previously and comparing the number who had died with the numbers expected. For each study environ-

TABLE 1: TERMS USED TO DESCRIBE MMMF PRODUCTS

European nomenclature		*US nomenclature*
Glass wool, Continuous filament	distinct products, but in US both classed as	Fibrous glass
Rock wool	classed as	Mineral wool

TABLE 2: OBSERVED AND EXPECTED NUMBERS OF DEATHS FROM RESPIRATORY CANCER* BY YEARS SINCE FIRST EXPOSURE AND TYPE OF FIBRE

	American Study				European Study**					
	Fibrous glass		Mineral wool		Glass wool		Continuous filament		Rock wool	
Years since first exposure	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
10-19	72	76	15	9	34	30	6	8	30	25
20-29	38	39	16	11	29	29	0	2	22	18
30+	47	36	14	8	17	12	0	0	12	7

* *Under this heading the European study includes only cancers of the trachea, bronchus and lung, whereas the American study takes into account other cancers of the respiratory tract as well.*

** *Simonato et al, 1986.*

TABLE 3: OBSERVED AND EXPECTED NUMBERS OF DEATHS FROM NON-MALIGNANT RESPIRATORY DISEASE* BY YEARS SINCE FIRST EXPOSURE AND TYPE OF FIBRE

	American Study				European Study**					
	Fibrous glass		Mineral wool		Glass wool		Continuous filament		Rock wool	
Years since first exposure	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
10-19	44	37	6	4	30	33	7	8	18	26
20-29	60	43	7	5	15	18	1	2	9	11
30+	25	20	8	5	3	5	2	1	11	8

* *The American study excludes influenza and pneumonia from this category.*

** *Saracci et al, 1984.*

mental surveys were carried out at most plants so that individual estimates of dose could be made. Expected numbers of deaths were calculated overall and by cause of death, the groups studied being subdivided by exposure and by years since first exposure to MMMF. There were however slight differences between the diseases included in the studies (see footnotes to tables 2 and 3) and between the terms used to describe the fibre produced in North America and Europe (summarized in table 1).

The American study

The American study (Enterline and Marsh, 1984) was started in 1974 and the 17 plants involved were among the oldest and largest then in operation: they represented the bulk of MMMF production in the USA between 1940 and 1952. The group studies included all men who had worked in production or maintenance for at least one year during the period 1945-63. Those who had worked with fine fibres (nominal diameter < 1.5μm) were of special interest and were therefore included if they had worked for at least six months. Environmental surveys were made in 16 of the 17 plants (Esmen *et al*, 1979) and for purposes of estimating dose respirable fibres were defined as those of diameter less than 3μm, as measured by optical microscope. On the basis of information about changes of fibre size, ventilation, housekeeping and working practices it was generally assumed that exposure levels had been similar in the past. To calculate the doses to individuals the fibre concentrations at each job and each time were summed over the length of time it took to do the job. The average exposure levels were 0.04 fibres/ml in the 11 fibrous glass plants and 0.35 fibres/ml in the six mineral wool plants. The highest average exposure was 1.5 fibres/ml.

In all 14,884 fibrous glass workers and 1846 mineral wool workers were included in the study, and for only 336 of them (2.0%) was it not known whether or not they were still alive. 3761 were known to have died, death certificates being available for 3653 (97.1%). The expected numbers of deaths were calculated from the death rates in the US white male population as a whole, without correcting either for regional variations in mortality or for the fact that a few (2%) of the population studied were not "white". Data relating to fibrous glass workers and to mineral wool workers were analysed separately.

American study: fibrous glass workers

There was a slight, though significant, deficiency of deaths overall (observed 3262, expected 3391) but neither the study population as a whole nor any sub-group of it showed evidence of there being more or fewer cancers than expected. For respiratory diseases other than cancers a significant deficiency of deaths due to influenza and pneumonia was offset by an equal excess of deaths from other respiratory diseases.

There was no evidence that respiratory cancer was related either to cumulative fibre exposure or to duration of exposure to fibres, but those first employed in the MMMF industry 30 or more years previously had a higher respiratory cancer death rate (table 2). The excess of non-malignant lung disease (other than influenza and pneumonia) seems to be unrelated to cumulative exposure, to duration of exposure or (see table 3) to years since first exposure.

American study: mineral wool workers

For mineral wool plants the pattern appears rather different. Total mortality (observed 499, expected 468), respiratory cancer mortality and respiratory disease mortality were all raised, and in the case of respiratory cancer the excess was statistically significant. However the six mineral wool plants include the most westerly and the most southerly of all these studies and the higher death rates may reflect regional differences. Neither respiratory cancer nor non-malignant respiratory disease excluding influenza and pneumonia showed a clear relation with fibre exposure, with duration of exposure, or (see tables 2 and 3) with years since first exposure.

The European study

Although the European study (Saracci *et al*, 1984; Simonato *et al*, 1986) seems very similar to the American one its effective coverage was more limited, because of difficulties in obtaining the required information. These were of various types. Thus in some countries it proved difficult to obtain death certificates and some factories had to be excluded because the records were inadequate or because asbestos had also been processed there. As a result, out of 72 MMMF plants in 15 countries

TABLE 1: TERMS USED TO DESCRIBE MMMF PRODUCTS

European nomenclature		*US nomenclature*
Glass wool, Continuous filament	distinct products, but in US both classed as	Fibrous glass
Rock wool	classed as	Mineral wool

TABLE 2: OBSERVED AND EXPECTED NUMBERS OF DEATHS FROM RESPIRATORY CANCER* BY YEARS SINCE FIRST EXPOSURE AND TYPE OF FIBRE

	American Study				European Study**					
	Fibrous glass		Mineral wool		Glass wool		Continuous filament		Rock wool	
Years since first exposure	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
10-19	72	76	15	9	34	30	6	8	30	25
20-29	38	39	16	11	29	29	0	2	22	18
30+	47	36	14	8	17	12	0	0	12	7

* *Under this heading the European study includes only cancers of the trachea, bronchus and lung, whereas the American study takes into account other cancers of the respiratory tract as well.*

** *Simonato et al, 1986.*

TABLE 3: OBSERVED AND EXPECTED NUMBERS OF DEATHS FROM NON-MALIGNANT RESPIRATORY DISEASE* BY YEARS SINCE FIRST EXPOSURE AND TYPE OF FIBRE

	American Study				European Study**					
	Fibrous glass		Mineral wool		Glass wool		Continuous filament		Rock wool	
Years since first exposure	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
10-19	44	37	6	4	30	33	7	8	18	26
20-29	60	43	7	5	15	18	1	2	9	11
30+	25	20	8	5	3	5	2	1	11	8

* *The American study excludes influenza and pneumonia from this category.*

** *Saracci et al, 1984.*

mental surveys were carried out at most plants so that individual estimates of dose could be made. Expected numbers of deaths were calculated overall and by cause of death, the groups studied being subdivided by exposure and by years since first exposure to MMMF. There were however slight differences between the diseases included in the studies (see footnotes to tables 2 and 3) and between the terms used to describe the fibre produced in North America and Europe (summarized in table 1).

The American study

The American study (Enterline and Marsh, 1984) was started in 1974 and the 17 plants involved were among the oldest and largest then in operation: they represented the bulk of MMMF production in the USA between 1940 and 1952. The group studies included all men who had worked in production or maintenance for at least one year during the period 1945-63. Those who had worked with fine fibres (nominal diameter < 1.5μm) were of special interest and were therefore included if they had worked for at least six months. Environmental surveys were made in 16 of the 17 plants (Esmen *et al*, 1979) and for purposes of estimating dose respirable fibres were defined as those of diameter less than 3μm, as measured by optical microscope. On the basis of information about changes of fibre size, ventilation, housekeeping and working practices it was generally assumed that exposure levels had been similar in the past. To calculate the doses to individuals the fibre concentrations at each job and each time were summed over the length of time it took to do the job. The average exposure levels were 0.04 fibres/ml in the 11 fibrous glass plants and 0.35 fibres/ml in the six mineral wool plants. The highest average exposure was 1.5 fibres/ml.

In all 14,884 fibrous glass workers and 1846 mineral wool workers were included in the study, and for only 336 of them (2.0%) was it not known whether or not they were still alive. 3761 were known to have died, death certificates being available for 3653 (97.1%). The expected numbers of deaths were calculated from the death rates in the US white male population as a whole, without correcting either for regional variations in mortality or for the fact that a few (2%) of the population studied were not "white". Data relating to fibrous glass workers and to mineral wool workers were analysed separately.

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only 13 in seven countries were regarded as acceptable for the study (four glass wool, two continuous glass filament and seven rock wool). For the statistical analysis expected deaths were calculated from national death rates. 2719 (12.4%) of the 21,967 people in the study population were known to have died by 1982. The expected number of deaths was 2457, but for reasons unknown there was a large number of accidental and violent deaths among workers exposed for less than one year.

Environmental studies were made at 12 of the 13 plants (Ottery *et al*, 1984). Respirable fibres were defined as longer than 5μm, finer than 3μm and with an aspect ratio of at least 3. The average concentration of respirable fibres was 0.02 fibres/ml for glass wool, 0.006 fibres/ml for continuous filament and 0.04 fibres/ml for rock wool. The highest concentration measured was 1.89 fibres/ml. There is however recent evidence that fibre counts should be multiplied by two or three (Gilson, personal communication).

During 1983 and 1984, the research team visited the 13 factories again and classified the production processes into three technological phases in each factory: "early", when no dust suppressing agent was used and/or there was a batch process involving labour intensive and hand-operated production; "intermediate"; and "late" when oil and resin binders were in use with modern mechanised production methods.

European study: mortality

The observed numbers of deaths exceeded the expected by about 10% independent of time since first exposure to MMMF. However, the lung cancer pattern was rather different with a marked excess among those first exposed at least 30 years earlier (observed deaths 29, expected 19).

Table 2 shows that among those first exposed at least 30 years ago in both glass wool and rock wool production there were five more lung cancer deaths than expected for people of the same age and living in the same locality. There were so few people who had worked that long in continuous filament production that only 0.3 deaths were expected and none observed.

Analysis by technological phase for those first exposed 30 or more years ago yields the following: early phase – observed deaths 21, expected 15; intermediate – observed 46, expected 36; and late – observed 13, expected 15.

The results in table 3 on mortality from non-malignant respiratory diseases are taken from Saracci *et al* (1984) with follow up to 1977 only as the later report considered total mortality and lung cancer only. There is no apparent association of mortality with type of MMMF or with years since first exposure. Similar analyses also showed no relation with duration of exposure.

Mesothelioma: American and European studies

The only case of mesothelioma in either study had been employed in a European rock wool plant for 92 days, some 11 years before his death. This case cannot be attributed causally to exposure to MMMF.

Other mortality studies

McDonald (1984) has reviewed various other mortality studies. Those published before the WHO conference on the effects of MMMF (held in 1982 and reported in 1984) constantly failed to provide evidence of excess respiratory cancer or of non-malignant respiratory disease, even for those first employed 30 or more years previously. In clear contrast to these results, however, both of the other studies of production workers reported at the WHO conference (Morgan *et al*, 1984; Shannon *et al*, 1984) yielded excess deaths from lung cancer (combined observed 44, expected 32).

Engholm *et al*, (1984) reported preliminary findings on the incidence of respiratory cancer among Swedish construction workers exposed to MMMF. Dust exposure during construction is probably several times higher than in production. In their complete follow-up study 286 respiratory cancers occurred compared with 290 expected. From a case-control study attempting to allow for possible exposure to asbestos, the authors conclude that there is an association with heavy exposure to MMMF (relative risk, 3.18) but not with heavy exposure to asbestos (relative risk, 0.75).

Discussion

The two major studies in America and Europe are amongst the largest epidemiological studies ever undertaken in occupational health. Even so the American study is too small to detect less than about a 30% extra respiratory cancer risk among those first employed 30 or more years ago. The European study is even less powerful because relatively few of those studied had worked in the industry before the late 1940s.

Combining all information from both studies gives a highly significant excess of respiratory cancer among those with 30 or more years since first exposure (observed deaths, 90, expected, 63). These figures compare with 157 observed deaths and 148 expected for those first exposed 10-19 years previously and with 105 observed and 99 expected for the intermediate group.

In view of the very low concentrations of airborne MMMF, this excess cannot be reconciled with expectation based, for example, on results from Quebec chrysotile asbestos miners if one assumes the excess to be causally related to fibre exposure only. On that assumption, MMMF are more hazardous than asbestos at its worst. Yet the animal inhalation experiments, the slight evidence of hazard among the Swedish construction workers and the existence of only one mesothelioma case in some 700,000 person years of observation all argue that MMMF do not approach the hazard of asbestos. This argument is also supported by the lack of any association of lung cancer mortality with fibre concentration.

Hence the assumption that the excess lung cancers are caused by MMMF only must be modified or rejected. The latest analysis of the European studies taking into account technological phase demonstrates that the excess is associated with the earlier phases only. Details of dust levels and of possible exposure to other toxic substances, such as bitumen, in early use as binders, are not yet available. It must be hoped that this information will be presented at the next WHO conference on MMMF in October this year.

These major studies have concentrated on the MMMF production industry. Clearly it is also essential to undertake good epidemiological studies in the MMMF-user industry,

where exposure to fibre is likely to have been at higher levels, to permit better exploration of putative dose-response relations.

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'In earlier times, they had no statistics and so they had to fall back on lies
Hence, the huge exaggerations

Fibrous silicate mineral fibres

1. Dose

measurement of material to which person is exposed.

(dose) - how many fibres reach the target organ & how long they are there.

Risk - only present in workplace / workplaces.

2. Relation

what pattern?

Response

dose

~~Toxicity~~

B: Urban. } pure asymptomatic disease
→ lung cancer

Analysis.

Complicated by age.

+ smoking

+ social class, etc.

social class 1 : professional

2 : technical & intermediate

3 : skilled manual

4 : partly skilled.

5 : unskilled labour.

Analyses are usually -

age - standardized.

=> standardized Mortality Ratio. (Prospective studies).

=> Mantel-Haenszel test (case-control studies)

Exposure

Disease		No	Yes (Low	Med.	High)	
	No	87	7	5	1	100
	Yes	25	19	17	12	73
		112	26	22	13	173

Asbestos ~~Cancer~~

Cigarette		No	Yes
	No	1	5
	Yes	10	50

Risk.

* Retrospective	-- Prospective.
- One disease	many diseases
- many exposures	one / few exposures
- Exposure evidence poor	Exposure data good ("fully" prospective) mixed ("retro" prospective).
- Disease evidence good	Disease evidence less good.
Quick to complete.	Time consuming
Smaller Study	Larger Study
May be more expensive. (cost of getting exposure data)	may be more expensive (larger study)
Disease can be defined at death or diagnosis — wide range	Disease can be defined at death or diagnosis — narrow range dependent on training facilities.

TUC Centenary Institute of Occupational Health

Study Design and Analysis

PRINCIPLES OF MEASUREMENT

Purpose of lecture:

To introduce some principles of measurement by example. There are no fixed rules, so the lecture is intended to provide food for thought.

Primary aim of measurement:

The main aim is to permit estimation of dose-response relations. For occupational health, this requires measurements of person, occupation and exposure. The detail required depends entirely on the questions being studied.

Measurement of person

Mortality information is often obtained directly from OPCS death certificates although case-finding studies can effectively be used for small studies. A major advantage of mortality as an index of response is that only the identity of those in the study group need be known.

Morbidity assessments by contrast require cooperation of each worker. However, much more information is obtainable by questionnaire, chest x-ray, lung function testing and so on. Thus morbidity data may give much more sensitive measures of response to hazard than do mortality data.

Descriptive information must also be collected. Basic data such as date of birth and sex can be obtained from personnel records. Other details must also be provided by the workers, mainly by questionnaire. The importance of standardized techniques can not be over-emphasized.

Measurement of occupation

Personnel records should provide the most reliable information, but often the detail is inadequate and past records are not kept. Medical records are generally too unreliable. Personal questionnaires can yield more detailed occupational histories but care needs to be taken to ensure that they are complete.

The amount of detail required depends on how much information is or will be available about exposure.

Measurement of exposure

The simplest measure of exposure is occupation, but there should also be some index of duration of employment. Ideally, the biologically effective dose should be measured taking into account exposure, retention, elimination, latency, etc. Practically, only exposure levels can be estimated and retrospectively it is usually only possible to guess past exposure levels based on sparse information.

Environmental sampling techniques depend on
what substance is being measured;
which component is relevant;
whether the effects are short-term or long-term;
whether average or peak exposures are critical.

In determining cumulative exposure, decisions on how to combine duration of exposure with concentration need to be taken.

Confounding factors, such as previous occupation and atopic status, may need to be considered.

Biological monitoring may be the required method of determining exposure (HSE regulations) or the only effective method of measuring response (deep-sea divers). Occasionally biological monitoring may measure dose better than any existing environmental sampling methods.

TUC Centenary Institute of Occupational Health

Study Design and Analysis

INTRODUCTION TO STATISTICS

Purpose of lectures

To introduce statistical principles, the ideas underlying statistical reasoning, the basis of significance tests, the types of result produced and the interpretation of such results.

Role of statistics

The practice of occupational health includes the comparison of sets of results or of an observation with previous results. Statistics provides a **set of tools** which may be used to aid evaluation not only of clinical and research observations, but also of published reports. When there is no doubt about the interpretation of an observation, these tools are not of use. But whenever there is doubt, statistics has a part to play. It is the science of dealing with variation so as to obtain summary results and to express confidence in these results.

Statistics and the 'Scientific Method'

The four main stages of the scientific method are Observation, New Hypothesis, Prediction and Verification. Often the verification is the observation for a further cycle. Although statistics is of use in all stages, it is particularly important in the second and fourth. We assume that the new hypothesis is set up to be knocked down (the Null Hypothesis) and then in the fourth stage we ask:

> **Do the results (verification) disagree with prediction from the Null Hypothesis?**

There will always be some discrepancy, simply because of chance circumstances. The appropriate statistical technique answers the question:

> **Is the discrepancy between result and prediction reasonably attributable to chance?**

If yes, then the Null Hypothesis is not contradicted. If no, the Null Hypothesis has been knocked down.

Estimation of the size of an effect

Typically, the end-point of a statistical analysis is the calculation of an **estimate** of the size of an effect (for example, the increase in mortality among an occupational group or the reduction in airborne concentration of a solvent vapour). The value of this estimate is not very informative without some indication of its accuracy. Thus

an effect should be described in terms of the estimate and its **confidence interval**, that is the range of values which is likely to contain the true value of the effect. If this confidence interval does not include the no-effect value predicted by the Null Hypothesis, then 'the results disagree with prediction' and the 'discrepancy between result and prediction cannot reasonably be attributed to chance'. If the confidence interval does include the no-effect value, then chance is a reasonable explanation for any discrepancy.

REMINDER: **Statistical methods are tools to provide summary results**

Probability

It is not possible to provide a confidence interval which certainly includes the true value of an effect (except by taking all possible values). Statistical techniques cannot give a Yes/No answer. Instead they provide a value, the **probability**, that the discrepancy is attributable to chance, assuming the Null Hypothesis to be true. This probability, **P**, varies between 0 (no chance) and 1 (certainty). Tradition, but tradition alone, dictates that the Yes/No dividing line is taken at 0.05 (5% probability). The term **statistically significant** is just shorthand for

> **If the Null Hypothesis is true, the discrepancy between result and prediction is so large that the probability of the occurrence of this discrepancy (or larger) is less than 5%.**

'Statistically significant' is the same as 'the confidence interval does not include the no-effect value'.

REMINDER: **Statistical methods are tools to aid evaluation**

Six cautions

1. Statistical significance does not confirm the reliability of a study.
2. The significance level (dividing line) should be stated.
3. Statistical significance need not imply practical significance.
4. Statistical significance is evidence, but not proof, that a real effect exists.
5. Absence of statistical significance is not proof (nor even evidence) that no real effect exists.
6. Statistical significance tells nothing about the nature of an association.

TUC Centenary Institute of Occupational Health

Occupational Epidemiology

Epidemiology is concerned with patterns of disease occurrence and the factors which influence these patterns.

Purposes

To elucidate the aetiology of a specific disease, using epidemiological data and information from other disciplines.

To evaluate the consistency of epidemiological data with existing aetiological concepts.

To provide the framework for developing and evaluating prevention procedures and public health practice.

Occupational epidemiology is an observational discipline (primarily). Groups of individuals are observed to discover the health status of the group and to relate this health status to prior occupational and environmental conditions.

Observation of an association between 'cause' and 'effect' does not prove that the 'cause' did cause the 'effect'. Much other information is required before causality can be inferred.

* Epidemiology

Epidemiology is concerned with

- patterns (ziekte) of human disease occurrence
- factors (risico's) which influence patterns

—

Does cigarette smoking cause cancer of the lungs?
X not strictly possible to answer just with yes — no.

—

General purpose

1. To elucidate (verjaardag) the aetiology of a specific disease (ziekteleer)
2. To evaluate (waarderen) the usefulness of epidemiology data (toepassingen)
3. To provide the basis for planning and evaluating preventive (preventieve) measures (maatregelen).

(1) Epidemiology is Observational

(with a little experimental).

(a) Epidemiology is Comparative

the comparison of groups

Inductive :-

Consider the hypothesis that exposure to asbestos causes lung cancer

Of the subjects, an individual can be

not exposed } not a lung cancer case
exposed } a lung cancer case

Whatever the state that individual tells nothing about ... (prospective).

Exposure

Retrospective ⟹ Disease		No	Yes	
	No	87	13	100
	Yes	25	(48)	(73)
		112	61	173

173 people studied
at one point in time
"cross-sectional study".

173 workers in an industry identified
at one point in time
at entry to industry } and followed forward (study).

Criteria for causation

Bradford Hill has succinctly summarised the evidence required to be able to draw the conclusion of causality in his Presidential Address to the new Section of Occupational Medicine of the Royal Society of Medicine in 1965.

The nine criteria he proposed are given below, together with a mnemonic devised by an earlier occupational health MSc student. You are strongly encouraged to read Bradford Hill's paper.

Strength of association	**S**tatistics
Consistency	**C**an
Specificity	**S**ometimes
Temporality	**T**each
Gradient of response	**G**ood
Plausibility	**P**rinciples.
Coherence of evidence	**C**an
Experimental evidence	**E**pidemiology
Analogy	**A**lso
	?

Reference: Bradford Hill, A. (1965) The environment and disease: association or causation? Journal of the Royal Society of Medicine, 58, 295-300.

Types of Epidemiological Studies

Cross-sectional

A study in which people are observed at one point in time only. Information about exposure obtained from memory or from personnel records or from industrial hygiene data.

Prospective study

A study in which people are identified at a point in time, their exposure is measured and they are followed forward to disease.

Retrospective study

A study in which people with disease are identified and investigated backward for evidence of exposure.

Analysis of epidemiological studies

Analyses are complicated by age, smoking habits, etc. These are called confounding factors.

So analysis is usually age-standardized, to calculate SMR (Standardized Mortality Ratio) for Prospective studies and Odds Ratio for Retrospective studies.

Environmental Health Criteria 27.

Guidelines on Studies in Environmental Epidemiology.

CARCINOGENICITY

A carcinogenicity study in which Carbadox and another compound were tested is described in a recent report from Czechoslovakia (Sykora & Vortel, 1986). Neonatal outbred Wistar rats of both sexes were divided into 25 test groups, with 5 to 18 animals per group. Some groups used in the part of the study concerned with Carbadox received the compound intraperitoneally from the day of birth, for the first 8 to 20 days of life; the doses used are not stated. In addition, Carbadox was added to the feed of some groups at a level of 300 ppm, after weaning (22 to 25 days after birth). Surviving animals were observed for up to 52 weeks.

The authors explain that the 'post-natal' regime has several advantages: very young animals lack some detoxifying enzymes; they do not show the inter-individual variations which characterise adult metabolism; rapidly growing tissues have a marked 'saturation function'.

In the test groups receiving Carbadox by the i.p. and oral routes, all but one animal developed malignant hepatomas. The livers of these animals contained numerous tumours, 25 in one case. In addition, all the animals which received Carbadox in the diet alone developed malignant hepatomas. The Carbadox-treated animals also showed an increased incidence of a variety of other malignancies, in addition to those affecting the liver, compared with controls.

Although this study is poorly reported and can be criticised on a number of grounds, it nevertheless demonstrates unequivocally that Carbadox is a potent carcinogen.

TRANSLATION

POST-NATAL STUDY OF THE CARCINOGENICITY OF CYADOX AND CARBADOX

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Introduction and literature review

Post-natal carcinogenicity tests are a very good way of determining the carcinogenicity of chemical substances on biological material. The resultant organisms represent a suitable basis for the biological detection of carcinogens, mainly as a result of the lack of some of the enzymes which are essential to the metabolic detoxification of foreign substances, but also through varying metabolism in adult individuals and, last but not least, the marked saturation function of rapidly growing organs and tissue (BOYLAND, 1968; SYKORA et al, 1984, 1985). We tested for post-natal carcinogenicity with known carcinogens, such as dimethylnitrosamine, diethylnitrosamine, 1,2-dimethylhydrazine dihydrochloride, etc.

Non-antibiotic growth stimulants of the quinoxaline type are among the most commonly used farm animal feed additives. In Czechoslovakia, the Cyadox stimulant has been developed, which is chemically very close to the commonly used Carbadox (BROZ et al, 1979). The mutagenic nature of Carbadox has been described by many authors (OUD et al, 1979; GANDALOVICOVA et al, 1980; YOSHIMURA et al, 1981; SYKORA et al, 1981; SRAM et al, 1983; HOLDA, 1984; POKORNA, 1984) and its hepatocarcinogenicity has also been discussed in several works (Pfizer Co., 1975; TRUHAUT et al, 1981; SYKORA et al, 1984). On the other hand, no marked mutagenicity has been demonstrated for Cyadox, nor has any carcinogenic effect been determined. We have now supplemented the available data with the results of post-natal carcinogenicity tests in which the Czechoslovak stimulant Cyadox is compared with Carbadox.

Method and materials

Conventional outbred Wistar rats were used as experimental material. We took the young rats from 27 females which were shown by vaginal smears to be pregnant. The date of birth and the sex of the young were recorded. They were weighed at birth (0 day) and again at 5, 10 and 20 days. They were weighed again after 7 weeks and then at fortnightly intervals until the end of the study. The experiment was brought to an end with the sacrifice and autopsy of the surviving animals after 52 weeks (i.e. 1 year). A total of 228 rats were weaned - 119 males and 109 females.

Both stimulants were administered intraperitoneally to the young rats from the first day following birth in the form of a 1:4 suspension with gum arabic in concentrations of 0.006% (solution A), 0.36% (solution B) and 0.5% (solution C) and in volumes of 0.1-0.3 ml per animal. We gave the control groups a suspension of gum arabic corresponding to

the parameters of group B. The doses are expressed as total doses for the entire administration period. Administration periods for the various groups were 8, 10, 15 and 20 days. With some groups, apart from the post-natal administrations, we also used 300 ppm concentrations of stimulants in feed after weaning (22-25 days after birth) until the end of the tests. Table 1 gives details of the various test groups.

We regularly checked all the animals during the tests and animals in which palpation examination led to the discovery of solid growths in the abdominal cavity or whose state of health deteriorated significantly were dissected in the pathology-anatomy department. Similarly, we examined all the animals which survived until the end of the tests and those which died during the tests. Any tumours were examined histologically. Samples of tumours were preserved in neutral 10% formalin. Histological samples were prepared using the normal paraffin technique and stained with haematoxyline-eosine or by some other means.

The rats were fed with a DOS-2b diet throughout the tests. After weaning, they were kept in T3 glass cages, with 2-3 animals of the same sex per cage, in conventional air-conditioned test stalls, with the temperature maintained at 21-26°C, atmospheric humidity at 55-80% and with a lighting scheme of 12 hours light and 12 hours darkness.

Results

Mortalities before weaning

In the three control groups, only 2 animals died (Table 2).

In the Cyadox group, seven animals died, the greatest percentage in group XXIV (30.7%). However, the overall percentage loss prior to weaning was less than for the control animals.

Carbadox showed a clear toxic effect. The highest number of deaths occurred in the groups given relatively high doses over a short period. All the animals in group V and over half those in group III died. The overall percentage loss was twice as much as for the control groups.

Survival until the end of the study

All the animals which were given intraperitoneal administrations of Cyadox or Carbadox survived until the end of the experiment, except for one female in group II, which died prematurely as a result of deformed incisors. Similarly, all the rats which, as well as the post-natal administration, were fed with a diet containing Cyadox, survived until the end of the experiment. And so did the animals in the two control groups fed with the stimulants after weaning until the end of the study and, of course, the animals in the first control group.

Tumours discovered in the abdominal cavity during palpation examinations were found almost equally in all the groups in which the rats were fed a diet including Carbadox in the post-natal period after weaning. Before the end of the tests, we dissected 16 rats, which represents 30.2% of the animals in the following groups:

XIX - 5.40 mg Carbadox, 1st-10th days - 2 rats, i.e. 20.0%
XXI - 7.50 mg Carbadox, 1st-15th days - 8 rats, i.e. 44.4%
XXIII - 0.27 mg Carbadox, 1st-20th days - 2 rats, i.e. 15.4%
XXV - 9.03 mg Carbadox, 1st-20th days - 4 rats, i.e. 33.3%

There is no obvious dependency upon amount or period of dosage. The age of the rats selected for pathological-anatomical examination before the end of the study because of abdominal cavity findings during palpation or because of deteriorating state of health varied between 43 and 51 weeks.

Weight gain

Effects on weight gain (Table 3) are expressed as percentage differences in average gain compared with control group I during the first three weeks (i.e. during post-natal administration) and then after weaning until the end of the tests. Even though the results are distorted by the different numbers of animals in the various groups, caused mainly by the different litter sizes or by the number of deaths, effects on the animals' weight can be inferred from these data. It is evident that during the first three weeks of the experiment growth was significantly reduced after administration of Cyadox in practically all groups except group II (C 1st-8th days, 3.96 mg) and group XXII (C 1st-20th days, 0.27 mg). Carbadox also affected weight gain before weaning in all groups except groups XI and XIII (K 1st-20th days, 0.27 mg and 5.43 mg). In comparison with Cyadox, there is a considerably more marked decrease in growth in the groups which were given Carbadox up to the 10th-15th days after birth (groups II, IV, VI and VIII as against groups III, VII and IX).

After weaning, a marked increase in weight gain was evident in practically all the test groups only treated with stimulants during the post-natal period in comparison with the control group. The average weight of the rats, which, after weaning, was considerably reduced in the test animals in comparison with the controls, became practically the same by the 23rd week of the experiment. The exceptions were all those groups given a post-weaning diet containing a 300 ppm concentration of Carbadox (XVII, XIX, XXI, XXIII and XXV). In practically all these groups, including the controls, the average weight of the rats up until the end of the study was considerably lower than parallel control I, and also growth was considerably less, especially up until the 23rd week. We have already demonstrated the negative effect of Carbadox on weight gain in rats in previous studies (SYKORA, 1977; SYKORA et al, 1984).

Pathological-anatomical and histopathological examination

A review of all the tumours found is given in Table 4. In view of the small number of animals in the individual groups and because no dependency on dose or duration was determined during post-natal administration, we evaluated all the test groups uniformly. The table shows that the control animals (group I) which were given a gum arabic suspension only during the post-natal period did not develop a single tumour throughout the whole of the first year of their lives. The same was true of the control group which,

after weaning, was fed a diet containing 300 ppm of Cyadox (group XVI). However, an absence of spontaneous tumours up to the age of one year is not the rule. In view of the fact that there was a relatively small number of animals in the two control groups, we also used further control rats of the same strain from two previous tests (SYKORA et al, 1985, in print) in order to evaluate spontaneous occurrences. We designated these control groups with letters A and B; 45.4% of the eleven rats in group A were found to have tumours, as were 25% of the rats in group B. Overall, we found nine tumours in the 35 control animals, representing an index of 0.26.

Post-natal administration of Cyadox did not lead to the development of dependent tumours in any of the groups. The tumours found in groups only given Cyadox in the post-natal period (II-XIV) and in groups which were also given Cyadox in their diet after weaning (XVIII-XXIV) were all benign tumours which, like adrenal gland ganglioneuromae and mesotheliomae of the tunica vaginalis testis, often occur spontaneously in rats of this strain (DEERBERG et al, 1980). The adrenal gland ganglioneuroma, which was found in one male in group XVIII, is considered to be a very rare tumour (HOLLANDER et al, 1976). DEERBERG et al (1980) did not find any examples of this tumour in their cohort of 640 rats. Over the last eight years, we have found this tumour in the adrenal glands of only 3 rats. It is very doubtful whether the ganglioneuroma, which can be ascribed to abnormal differentiation of the adrenal gland tissue during the embryonic period, developed as a result of the administration of Cyadox. A mesothelioma of the tunica vaginalis testis developed in one of the fourteen males in group XX. DEERBERG et al (1980) discovered spontaneous mesotheliomae in 1% (three cases in 304 males).

This tumour belongs to a group of relatively rare spontaneous tumours. Another feature of this tumour is that it develops in older rats. In 1981, DEERBERG et al published data concerning a set of thirteen mesothelioma cases. The youngest was a 27-month-old male and the oldest 45 months old. Since, in our case, we were dealing with a one-year-old male, at an age when this type of tumour does not normally occur, we cannot exclude the possiblity that the administration of Cyadox was a factor in the development of the mesothelioma. We have already discussed the suspected positive link between Carbadox and the development of mesotheliomae in an 18-month carcinogenicity study of Cyadox and Carbadox in rats (SYKORA et al, 1984).

The control rats which were given a 300 ppm concentration of Carbadox in their food, but no post-natal administration, all developed malignant hepatomae. Also, one male developed a mesothelioma of the tunica vaginalis testis and an atypical adenoma of the uterine glandules was discovered in the uterus of one female. The findings in this control group clearly demonstrate the powerful carcinogenic potential of perorally administered Carbadox.

These effects were found to be less noticeable when the same substance was administered only during the post-natal period (groups III-XV). Malignant hepatomae were only found in two rats. However, the number of spontaneous tumours in these groups was double that

found in the same groups with Cyadox (0.36 as against 0.18).

In groups which were given Carbadox in their diet following post-natal administration (groups XIX-XXV), malignant hepatomae developed in all males and females except one. The livers of all the affected rats were pervaded with varying numbers of tumorous nodes. The largest number was found in a female in group XXV, which had 25 of them. According to SCHAUER et al (1976), highly active hepatocarcinogens induce the development of multiple nodes. According to this rule, Carbadox can be considered to be a very potent carcinogen. It also appears that the development of further malignant and less common tumours was caused by the combination of post-natal and peroral administration of Carbadox. This is supported by the fact that these tumours, which occur spontaneously in rats in older age groups, are unusual during the first year of life. Numbered among these were carcinoma of the large intestine in two males, carcinoma of the salivary glands in one female, haemangiosarcoma of the hypodermis in one male, thymoma in two males and carcinoma of the uterine mucous membrane in one female. These tumours were in addition to malignant hepatomae. One male even had three malignant tumours - malignant hepatoma, adenocarcinoma of the large intestine and haemangiosarcoma of the hypodermis.

Discussion

Post-natal intraperitoneal administration of Cyadox did not cause any Cyadox-dependent tumours to develop in rats. During post-natal administration, weight gain and the average weight of the young rats were reduced, but accelerated growth after weaning meant that they caught up with the average weight of the controls by the 23rd week. Increased growth was also evident in succeeding weeks up until the end of the study. Practically the same results were obtained with groups given a 300 ppm concentration of Cyadox in their diet after weaning until the end of the experiment. Again, no Cyadox-dependent tumours were found and weight gain followed the same pattern.

Carbadox administered intraperitoneally to young rats during post-natal development displayed a toxic effect. As well as a marked reduction in body weight, a greater number of deaths occurred. After cessation of Carbadox administration in the 23rd week, the rats again began to grow more quickly and they caught up with the average weight of the control group. Malignant hepatomae, which were dependent on the stimulant administered, were found in two females given Carbadox during post-natal development. One of these cases was a female from group VII, to which a total dose of 7.5 mg of Carbadox was administered over a period of 15 days, and the other was a female from group XV, to which a total dose of 9.03 mg of Carbadox was administered over a period of 20 days. Also, there were practically double the number of spontaneous tumours in all groups given Carbadox during the post-natal period compared with the groups given Cyadox. The groups in which the rats were given a 300 ppm concentration of Carbadox in their food after weaning until the end of the experiment showed a marked reduction in average

weight and weight gain. This effect was equally evident in the group not given Carbadox during post-natal development (group XVII). The development of malignant hepatomae was found in practically 100% of animals in groups given Carbadox in their diet after weaning, including the control group. Also, we recorded other malignant and less common tumours in these groups.

In order to give a better representation of the development of these malignant hepatomae and other tumours in relation to the individual groups, we calculated development as a percentage of dissected rats (Table 5). Table 5 shows that the development of malignant hepatomae is dependent upon the administration of Carbadox. "Other tumours" includes both spontaneous tumours and those mentioned in the preceding section.

In groups given Carbadox during the post-natal period, the number of spontaneous tumours was practically double that found in the two groups given Cyadox (30.7% v 17.9% and 16.6%).

The largest number of spontaneous and less common tumours was found in groups to which Carbadox was administered both post-natally and in the diet. When administered in the food only (group XVII), it caused approximately the same increase in spontaneous tumours as in groups to which it was administered in the post-natal period (25.0% v 30.7%). Against this, for all groups in which the rats were also given Carbadox during the post-natal period, the percentage of other tumours was again double that of the previous group (62.2% v 30.7%). In this set of rats, as well as spontaneous tumours, chiefly of the endocrine system, there were also some malignant and less common tumours, which can be related to the Carbadox administered.

It can be seen that Carbadox added to the food has a high hepatocarcinogenic effect in rats, much higher than for simple intraperitoneal administration up to the age of 20 days. On the other hand, the post-natal administration of Carbadox markedly accelerates the formation of spontaneous tumours and, when combined with administration in the diet, it can be seen to be the initiating factor in the development of a wide variety of other malignant tumours in various organs and tissues.

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a zároveň v kombinaci s přidáváním do krmiva se projevuje jako iniciační faktor podporující vznik široké palety dalších zhoubných nádorů v různých orgánech a tkáních.

Souhrn

V postnatální karcinogenní studii na krysách byly testovány stimulátory růstu hospodářských zvířat cyadox a carbadox. Obě látky jsme podávali od prvního dne po narození maximálně do 20. dne věku intraperitoneálně v suspensi s arabskou gumou v celkových dávkách od 0,27 do 10,8 mg. Část krys jsme po odstavu navíc krmili dietou obsahující cyadox nebo carbadox v koncentraci 300 ppm. Maximální délka studie byla 52 týdnů (1 rok).

Cyadox neprokázal v žádné pokusné skupině karcinogenní účinek.

Carbadox prokázal výrazný hepatokarcinogenní účinek. Pouze postnatální podávání carbadoxu vedlo ke vzniku maligních hepatomů u 5,1 % krys se současným zvýšením výskytu spontánních nádorů téměř u 31 % zvířat. Jeho přidávání do diety vyvolalo téměř 100% výskyt maligních hepatomů a v kombinaci s postnatálním podáváním se zároveň zvýšil počet spontánních i dalších zhoubných a méně obvyklých nádorů, které lze dávat také do vztahu k působení carbadoxu.

Klíčová slova: cyadox, carbadox, krysy, postnatální karcinogenita

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Tabulka 1 — Přehled pokusných skupin, délka aplikace během postnatálního období, použitá koncentrace a celková podaná dávka v mg/mládě / Table 1 — A survey of test groups, lenght of administration during postnatal period, concentration used and total dose (mg per young)

Skupina Group	Podávaná látka Substance administered	Počet krys Number of rats	Délka aplikace Lenght of administered (dny / days)	Koncentrace a objem / Concentration and volume (ml) 1.—5.	6.—10.	11.—15.	16.—20.	Celková podaná dávka Total dose administered (mg)
I	Kontrola / Control	8	20	0,1	0,2	0,3	0,3	0
II	Cyadox	10	8	B—0,1	B—0,1	—	—	3,96
III	Carbadox	5	8	B—0,1	B—0,1	—	—	3,96
IV	Cyadox	10	10	C—0,1	C—0,2	—	—	7,50
VI	Cyadox	8	15	C—0,1	C—0,1	C—0,1	—	7,50
VII	Carbadox	7	15	C—0,1	C—0,1	C—0,1	—	7,50
VIII	Cyadox	10	15	B—0,1	B—0,2	B—0,3	—	10,80
IX	Carbadox	2	15	B—0,1	B—0,2	B—0,3	—	10,80
X	Cyadox	12	20	A—0,1	A—0,2	A—0,3	A—0,3	0,27
XI	Carbadox	8	20	A—0,1	A—0,2	A—0,3	A—0,3	0,27
XII	Cyadox	6	20	B—0,1	B—0,1	B—0,1	B—0,1	7,20
XIII	Carbadox	8	20	A—0,1	B—0,1	B—0,1	B—0,1	5,43
XIV	Cyadox	11	20	B—0,1	B—0,1	B—0,2	B—0,2	10,80
XV	Carbadox	9	20	A—0,1	B—0,1	B—0,2	B—0,2	9,03
Skupiny krmené po odstavu dietou obsahující C nebo K v koncentraci 300 ppm / Groups given a diet containing cyadox (C) or carbadox (K) at a concentration of 300 ppm after weaning								
XVI	Kontrola / Control + C	5	20	0,1	0,2	0,3	0,3	0
XVII	Kontrola / Control + K	8	20	0,1	0,2	0,3	0,3	0
XVIII	Cyadox + C	8	10	B—0,1	B—0,2	—	—	5,40
XIX	Carbadox + K[a]	10	10	B—0,1	B—0,2	—	—	5,40
XX	Cyadox + C	23	15	C—0,1	C—0,1	C—0,1	—	7,50
XXI	Carbadox + K[b]	18	15	C—0,1	C—0,1	C—0,1	—	7,50
XXII	Cyadox + C	8	20	A—0,1	A—0,2	A—0,3	A—0,3	0,27
XXIII	Carbadox + K[c]	13	20	A—0,1	A—0,2	A—0,3	A—0,3	0,27
XXIV	Cyadox + C	9	20	A—0,1	B—0,1	B—0,2	B—0,2	9,03
XXV	Carbadox + K[a]	12	20	A—0,1	B—0,1	B—0,2	B—0,2	9,03

C — cyadox; K — carbadox

Koncentrace suspenze stimulátorů pro subkutánní aplikaci: / Stimulant suspension concentration for subcutaneous administration:
A = 0,006 % B = 0,36 % C = 0,5 %

Tabulka 2 — Přehled úhynu mláďat krys do odstavu v jednotlivých dávkách po postnatální aplikaci cyadoxu a carbadoxu / Table 2 — A survey of the mortality of young rats before weaning according to the cyadox and carbadox dose administered in the postnatal period

Skupina Group	Podávaná látka a cesta aplikace Substance of care administration	Počet narozených Number born	Počet odstavených Number weaned	Úhyn Number of dead young	Procento úhynu Mortality percentage	Průměrný úhyn ve dnech Average mortality by days
I	Kontrola Control	9	8	1	11,1	12,0
II	C 1.—8.	12	10	2	16,6	8,0
IV	C 1.—10.	10	10	0	—	—
VI	C 1.—15.	8	8	0	—	—
VIII	C 1.—15.	10	10	0	—	—
X	C 1.—20.	12	12	0	—	—
XII	C 1.—20.	6	6	0	—	—
XIV	C 1.—20.	12	11	1	8,3	10,0
III	K 1.—8.	12	5	7	58,3	8,6
V	K 1.—10.	6	0	6	100,0	10,8
VII	K 1.—15.	9	7	2	22,2	12,5
IX	K 1.—15.	3	2	1	33,3	17,0
XI	K 1.—20.	8	8	0	—	—
XIII	K 1.—20.	8	8	0	—	—
XV	K 1.—20.	9	9	0	—	—
Skupiny krmené po odstavu dietou obsahující C nebo K v koncentraci 300 ppm / Groups given a diet containing cyadox or carbadox at concentration of 300 ppm after weaning						
XVI	Kontrola / Control + C	5	5	0	—	—
XVIII	C 1.—10. + C	8	8	0	—	—
XX	C 1.—15. + C	23	23	0	—	—
XXII	C 1.—20. + C	8	8	0	—	—
XXIV	C 1.—20. + C	13	9	4	30,7	12,2
XVII	Kontrola / Control + K	9	8	1	11,1	7,0
XIX	K 1.—10. + K	11	10	1	9,1	11,0
XXI	K 1.—15. + K	18	18	0	—	—
XXIII	K 1.—20. + K	13	13	0	—	—
XXV	K 1.—20. + K	13	12	1	7,7	6,0
	Kontrola / Control	23	21	2	8,7	9,5
	Cyadox	122	115	7	5,7	10,7
	Carbadox	110	92	18	16,3	10,2

Tabulka 3 — Přírůstek hmotnosti v procentech proti souběžné kontrole (I. skupina) / Table 3 — Weight gain, percent of parallel control (group I)

Skupina / Group	Podávaná látka délka aplikace Substance of days administration	Týdny / Weeks			
		0—3	3—23	23—51	3—51
II	C 1.—8.	— 7	+12	+65	+21
IV	C 1.—10.	—22	— 2	+41	+ 6
VI	C 1.—15.	— 8	+ 8	+80	+20
VIII	C 1.—15.	—26	— 4	+24	+ 1
X	C 1.—20.	—19	— 5	+35	+ 2
XII	C 1.—20.	—24	—12	+13	— 7
XIV	C 1.—20.	—33	+ 9	+12	+ 9
III	K 1.—8.	—42	— 3	+32	+ 3
VII	K 1.—15.	—38	—14	— 1	—11
IX	K 1.—15.	—21	+ 4	+59	+18
XI	K 1.—20.	— 7	0	+49	+ 9
XIII	K 1.—20.	— 1	+ 1	+41	+ 8
XV	K 1.—20.	—17	— 1	+20	+ 5
Skupiny krmené po odstavu dietou obsahují C nebo K v koncentraci 300 ppm / Groups given a diet containing cysdox (C) or carbadox (K) at a concentration of 300 ppm after weaning					
XVI	Kontrola / Control + C	—14	— 2	—11	— 4
XVIII	C 1.—10. + C	—14	+ 1	+46	+ 9
XX	C 1.—15. + C	—16	— 3	+51	+ 7
XXII	C 1.—20. + C	+13	—11	— 2	— 9
XXIV	C 1.—20. + C	—28	+ 1	+36	+ 7
XVII	Kontrola / Control + K	— 3	—19	—25	—20
XIX	K 1.—10. + K	—27	—20	— 5	—17
XXI	K 1.—15. + K	—40	—13	—11	—12
XXIII	K 1.—20. + K	—20	—11	— 6	— 8
XXV	K 1.—20. + K	—25	—17	—29	—19

C — cysdox; K — carbadox

Tabulka 4 — Nádory zjištěné u krys v jednotlivých skupinách / Table 4 — Tumours found in the rats in different groups

Druh nádoru / Tumour type	Kontrola Control I	Kontrola Control A	Kontrola Control B	Cyadox II–XIV	Kontrola Control + C XVI	Cyadox + C XVIII–XXIV
Počet krys / Number of rats	8	11	16	67	5	48
Adenom hypofýzy / Adenoma of hypophysis		1	3	4		
Adenom kory nadledviny / Adenoma of the adrenal cortex		1		1		1
Alveolární adenom plic / Alveolar adenoma of the lung			1			
Lymfangiom uzliny / Lymphangioma of a node		2		4		2
Polyp děložní / Uterine polyp		1				
Ganglioneurom nadledviny / Ganglioneuroma of the adrenal gland						1
Fibroadenom prsní žlázy / Fibroadenoma of the mammary gland				1		2
Cholangiom jater / Cholangioma of the liver				2		
Haemangiom sleziny / Haemangioma of the spleen						1
Mesothelíom obalu varlete / Mesothelioma of tunica vaginalis testis						1
Celkem / Total	0	5	4	12	0	8
Počet nádorů/krysu / Number of tumours/rat	0	0,45	0,25	0,18	0	0,16

Tabulka 4 — pokračování / Table 4 — continuation

Druh nádoru / Tumour type	Kontrola Control I	Kontrola Control A	Kontrola Control B	Carbadox III–XV	Kontrola Control + K XVII	Carbadox + K XIX–XXV
Počet krys / Number of rats	8	11	16	39	8	53
Adenom hypofýzy / Adenoma of hypophysis		1	3			1
Adenom kory nadledviny / Adenoma of the adrenal cortex		1				2
Alveolární adenom plic / Alveolar adenoma of the lung			1	2		1
Lymfangiom uzliny / Lymphangioma of a node		2		6		3
Polyp děložní / Uterine polyp		1				
Feochromocytom nadledviny / Adrenal phaeochromocytoma						1
Ca štítné žlázy / Ca of the thyroid gland				1		
Hepatom maligní / Malignant hepatoma				2	8	52
Ca tlustého střeva / Ca of the large intestine						2
Ca slinné žlázy / Ca of the salivary gland						1
Ca děložní sliznice / Ca of uterine mucous membrane						1
Haemangiosarkom podkoží / Haemangiosarcoma of the hypodermis						1
Mesothelíom obalu varlete / Mesothelioma of tunica vaginalis testis					1	
Fibroadenom prsní žlázy / Fibroadenoma of the mammary gland						6
Adenom sliznice děložní / Adenoma of the endometrium					1	1
Fibrom děložní / Uterine fibroma				1		
Haemangiom / Haemangioma				1		6
Cholangiom jater / Cholangioma of the liver				1		3
Thymom / Thymoma						2
Neurofibrom / Neurofibroma						1
Keratoakantom / Keratoacanthoma						1
Celkem / Total	0	5	4	14	10	85
Počet nádorů/krysu / Number of tumours/rat	0	0,45	0,25	0,36	1,25	1,60

Tabulka 5 — Absolutní a procentuální výskyt maligních hepatomů a ostatních nádorů v jednotlivých skupinách / Table 5 — Absolute and relative occurrence of malignant hepatomas and other tumours in the different groups

Podávaná látka Substance administered	Způsob aplikace Method of administration	Skupina Group	Počet krys Number of rats	Hepatom maligní Malignant hepatoma počet number	%	Ostatní nádory Other tumours počet number	%	Celkem nádory Tumours total počet number	%
Kontrola / Control	–	I + A + B	35	0	–	9	25,7	9	25,7
Kontrola / Control + C	D	XVI	5	0	–	0	–	0	–
Cyadox	PN	II–XIV	67	0	–	12	17,9	12	17,9
Cyadox + C	PN + D	XVIII–XXIV	48	0	–	8	16,6	8	16,6
Kontrola / Control + K	D	XVII	8	8	100,0	2	25,0	10	125,0
Carbadox	PN	III–XV	38	2	5,1	12	30,7	14	35,9
Carbadox + K	PN + D	XIX–XXV	53	52	98,1	33	62,2	85	160,4

C — cyadox; K — carbadox

D — podávání zkoušené dávky v dietě po odstavu / D — the tested substance administered in diet after weaning

PN — podávání zkoušené látky během postnatálního období intraperitoneálně / PN — the tested substance administered intraperitoneally during the postnatal period

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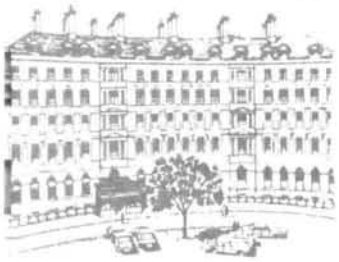

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THE MUTAGENICITY & CARCINOGENICITY OF CARBADOX

Dr G. E. Diggle

Introduction

Carbadox is a quinoxaline-di-N-oxide derivative, the full chemical name being methyl 3-(quinoxalinyl methylene) carbazate-N^1-N^4-dioxide. It possesses some antibacterial properties and was formerly used in the UK as a veterinary medicine for the treatment of bacterial enteritis in young pigs. At a later stage it was marketed for a period in this country as a 'growth promoter' for use in pigs.

All products containing Carbadox are now banned in the UK, as a result of a Prohibition Order under the Medicines Act 1968. This order prevents the sale and supply of all 'therapeutic' as well as growth-promoting products containing the compound.

Although Carbadox products, whether for therapy or growth promotion, are regarded in the UK as medicines (and are therefore subject to control under the Medicines Act), this is not the case in certain European countries, where they continue to be marketed as animal feedingstuffs used for growth promotion. The European Directive which controls animal feedingstuffs has been amended recently, with the effect that all Member States will, from 30 November 1987, be obliged to permit the free (off-prescription) sale of Carbadox growth promoters.

Very little information about the toxicological testing of Carbadox has been published in the scientific literature, and very little has been disclosed at open scientific meetings. Any data which may have been submitted to the UK regulatory authorities are subject to strict confidentiality requirements. Nevertheless reports of various mutagenicity studies and of a single carcinogenicity study have been published and these are discussed below.

MUTAGENICITY

Carbadox is strongly mutagenic to bacteria. It induces both frameshift and base-pair mutations in standard plate assays using Salmonella typhimurium, either with or without the addition of a metabolic activation mixture (Bentin et al, 1981; Yoshimura et al, 1981; Voogd et al, 1980; Negishi et al, 1980; Ohta et al 1980).

The effects in bacteria were confirmed by results obtained in the Luria-Delbruck 'fluctuation' assay using Klebsiella pneumoniae, in which extremely low concentrations of Carbadox were mutagenic (as little as 0.00005 m-mole/litre, whereas 0.005 m-mole/litre of 4-nitroquinoline-1-oxide were required to produce the same doubling of the spontaneous mutation rate). A positive result was also obtained using Escherichia coli (Voogd et al, 1980).

Carbadox has also been found to be strongly mutagenic to S.typhimurium strain TA 100 in host-mediated and urinary assays (Shirasu et al, 1978). Positive results were also reported in bacterial DNA repair 'rec' and 'uvr' assays (Bentin et al, 1981; Yoshimura et al, 1981; Ohta et al, 1980).

In a test system using strain D4 of the yeast Saccharomyces cerevisiae, an increase in mitotic gene conversion was produced by a concentration of 0.02% Carbadox in the culture medium (Voogd et al, 1980).

The foregoing findings clearly establish the potent genotoxic properties of Carbadox in a wide range of in-vitro systems. However although the results cause a considerable degree of concern, it is essential to establish whether the strong mutagenicity demonstrated in in-vitro testing is also reflected in the intact mammal. Fortunately a number of studies in rodents have been published. In a study using the mouse, Carbadox was administered orally as a single dose of 50, 100 or 200 mg/kg. Chromosome aberrations were induced in bone marrow cells at 100 and 200 mg/kg (Cihak & Vontorkovja, 1983).

A single intra-peritoneal injection of 210 mg/kg Carbadox was administered to mice (Oud et al 1979). At times 24, 30 & 36 hours after dosing, 50 metaphase cells from each of 5 animals were examined. Chromatid aberrations (breaks) were significantly increased and the maximum effect was seen 30 hours after dosing.

In a micronucleus study using the male Wistar rat, single doses of 5, 10, 15, 30, 60, 90, 120 or 240 mg/kg were administered, 30 and 6 hours before sacrifice. Over the whole dose range, Carbadox induced statistically significant increases in the number of micronucleated polychromatic erythocytes in bone marrow. At doses of 30 mg/kg and above there was evidence of marrow depression as well as genotoxicity (Cihak et al, 1983).

A micronucleus study was also carried out in themouse, following the intra-peritoneal injection of 52.5, 105, 210 or 525 mg/kg Carbadox. Again significant increases in the numbers of micronucleated polychromatic erythrocytes were seen; these effects were dose-related (Oud et al, 1979).

In a dominant lethal assay using the mouse, a positive result was obtained when Carbadox was tested in this system (Cihak et al, 1983). As the dominant lethal assay is a relatively insensitive test, a clear positive result (which indicates that serious damage to the genetic material of reproductive cells has occurred) is of especial significance.

In summary Carbadox causes gene mutations in a wide range of standard in-vitro systems, without the need for metabolic activation. The strongly genotoxic porperties observed in the absence of metabolising enzymes are also present when they are added. In intact animals, too, marked mutagenic properties persist and pronounced clastogenic effects are seen. The positive result in a dominant lethal assay is of particular significance.

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Dr (Mrs)
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Test of mutagenicity

1st level – do not need much samples beforehand.

Invetro – cytogenetic – good
- long how to do test
- serious ~~positive~~ results

- what human exposure (that depends on)

complex & combined – result

correlation with cancer → carcinogen

diet in – Carcinogens (possible) – kind of tumors in mouse.

CASE STUDY

MUTAGENICITY

DICHLORVOS

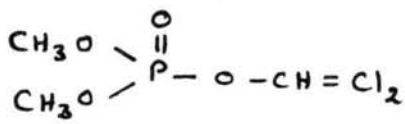
INTRODUCTION

Dichlorvos is an organophosphorus insecticide that is manufactured by many companies throughout the world, and has been widely used since the mid-1960s. The insecticidal properties of organophosphorus compounds are due to inhibition of cholinesterase. Dichlorvos is used for the control of household and public health insect pests, the control of insect pests in stored food and animal houses, and the control of spider mites and other insects in a range of greenhouse crops. It has rapid 'knock-down' and a major use has been in slow release generators (resin strips) for the control of flying insects in domestic houses and farm buildings. Average levels of dichlorvos in houses arising from such use are around 0.04 μg/l for the first 1-2 weeks post instillation, reducing to 0.01 μg/l after 3 months.

Concern has arisen about the possible genotoxicity of this compound because it is a known alkylating agent, and is mutagenic to micro organisms in vitro. The significance of these observations is considered in this case study.

PHYSICO-CHEMICAL PROPERTIES

Structure



Molecular formula and molecular weight

$C_4 H_7 Cl_2 O_4 P$ 221

Chemical name

BSI / ISO Common Name : dichlorvos

IUPAC Name : 2,2-dichlorovinyl dimethyl phosphate

Chemical Abstracts name : 2,2-dichloroethenyl dimethyl phosphate

CAS No. 62-73-7

Mutation

- [illegible] disease — cancer (body cells)

somatic mutation.
damage to DNA (genotoxic chem.)
→ may be mutation

Produce: Permit use to continue
PC evaluate: ? % local exposure risk!
- in kol conc. list
- slightly water
- DNA metabolites.

Public:

It is a colourless to amber liquid, with aromatic odour and boiling point 84°. It is miscible with alcohol and most non-polar solvents, and has appreciable solubility in water (about 1% at 20°).

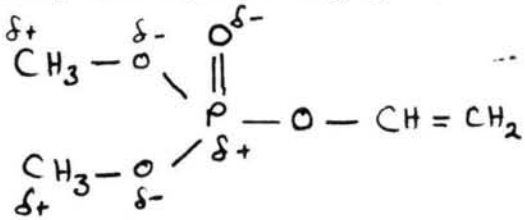
It hydrolyses slowly in water at 20° ($t1/_2$ ca 60 days), but much more rapidly in hot water ($t\ 1/_2$ 25 minutes at 70°) and in alkaline solutions. The hydrolysis products are dimethyl hydrogen phosphate and dichloroacetaldehyde. (see later section on metabolism).

Its vapour pressure is 1.6 Pa (about 1.2×10^{-2} mm mercury) at 20° and 3.9 Pa (about 2.9×10^{-2} mm) at 30°.

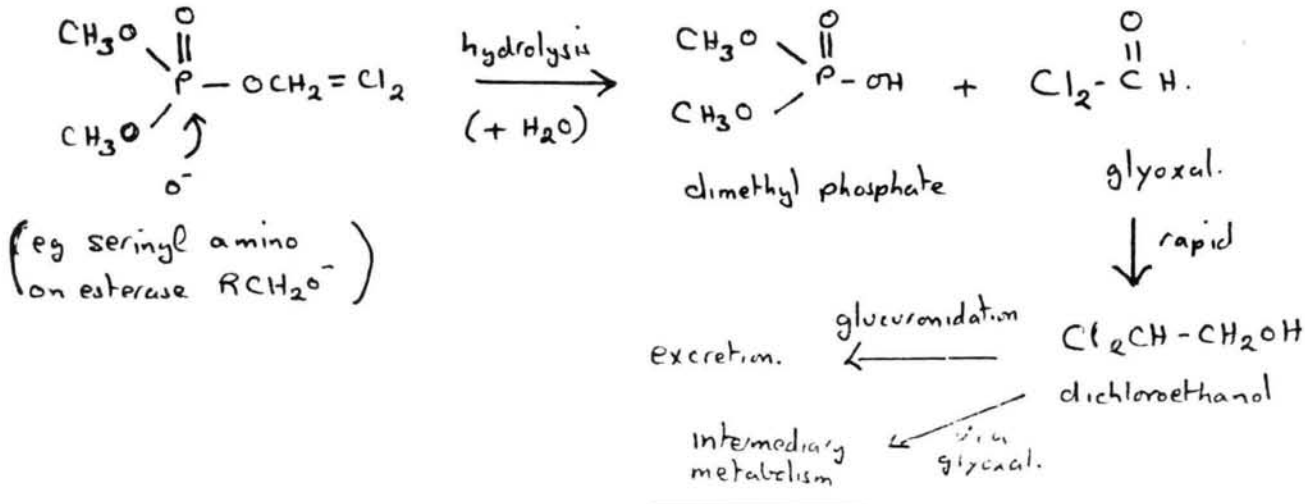
Its specific gravity is 1.415 at 25°.

METABOLIC DATA

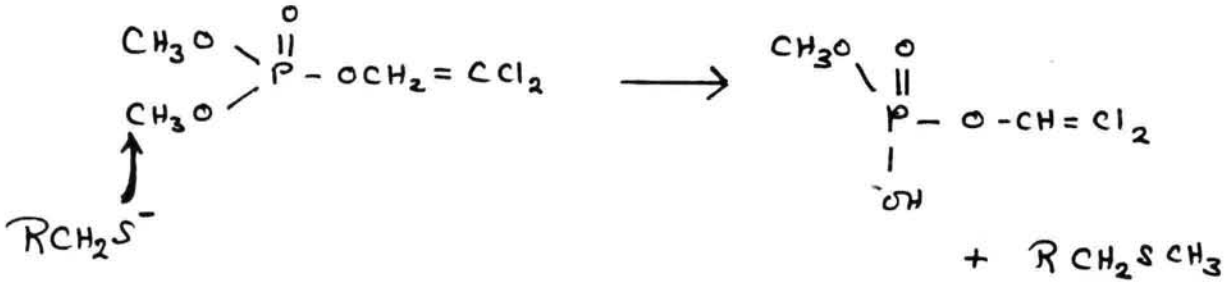
Dichlorvos is very rapidly broken down in mammals in vivo by various enzyme systems. The enzymic (and chemical) reactivity of dichlorvos can be explained by the electrophilic ($\delta+$) centres at the phosphorus atom of the phosphoryl group, and at the methyl carbons, both of which are susceptible to attack by neuleophiles (eg $-O^-$):-



The most important pathway of metabolism is by esterase catalysed hydrolysis. Esterases are very widely distributed in tissues of mammals, including blood. The initial products are dimethylphosphate and dichloroacetaldehyde. However, the latter compound has only a transient existence, and has not been detected in vivo, due to its rapid conversion to dichloroethanol. This is excreted as the glucoronide, or is converted to a dehalogenated 2 carbon fragment (possibly glyoxal) which enters the normal pathways of intermediary metabolism.



An alternative pathway is via attack on a methyl carbon resulting in demethylation, the enzyme involved being S-methyl transferase which catalyses transfer of a methyl group to glutathione, giving rise to S-methyl glutathione and demethyl dichlorvos.



Demethylation may also arise from the action of a microsomal oxygenase, which catalyses oxygenation at a methyl carbon to give rise to formaldehyde and demethyl dichlorvos, but this has only been demonstrated in vitro .

Thus dichlorvos is very rapidly broken down in vivo by several enzyme systems, but primarily by esterases which are present in blood and essentially all tissues. It has proved very difficult to actually detect any blood or tissue levels of dichlorvos following exposure by any route. For example no dichlorvos could be detected in rat blood or tissues using highly sensitive methods of detection following exposure to atmospheric levels of 0.5 g/l (about 10 times the maximum in-use levels arising from resin impregnated strips) for 14 days. The lowest concentration producing detectable levels, and then only in the kidneys of male rats (0.07mg/kg tissue) was 10 g/l in air for 4 hours.

TOXICITY

Dichlorvos has appreciable acute toxicity oral LD_{50} values in the range of 56-80 mg/kg being reported in rats and 100-300 mg/kg in dogs. It is well absorbed through the skin, the percutaneous LD_{50} being comparable to that obtained by the oral route, values of 75mg/kg being reported in rats and 107mg/kg in rabbits.

In a chronic dietary study in rats (2 years) no effects, other than cholinesterase inhibition, were reported at a level of 100 ppm in the diet.

GENETIC TOXICITY

Methylation of DNA

Dichlorvos has been shown to possess relatively weak alkylating activity, and can methylate DNA, the predominant site being the N-7 atom of guanine, with only very small amounts of O-6 alkylation (several hundred fold less than the N-7 site). The mechanism was similar to that seen with the 'classical' methylating agent methyl methane sulphonate (MMS), but the reaction was quantitatively much less effective, the rate of methylation of isolated DNA being 10-15 fold less, and that of cellular DNA 20-50 times less, than with MMS.

In vivo studies to investigate methylation of DNA in tissues in rodents have usually given negative results. Traces of methylated DNA have occasionally been seen following exposure to high doses of dichorvos, with only the N-7 methyl guanine being detected. Furthermore the methylated DNA was very short-lived, the $t_{1/2}$ being 1 minute of less.

MUTAGENICITY

In vitro studies

Studies in micro organisms

There is much evidence that dichlorvos produces mutations in micro-organisms, positive results being obtained in a range of different systems. The data obtained using strains of Salmonella typhimurium indicate that dichlorvos produces base-pair substition. Results in various strains of E.Coli suggest that the mutation process is largely error prone, the pattern of response being qualitatively similar to that seen with MMS, although potency as a bacterial mutagen is much less (20-100 times) than MMS (this reflects the lower alkylation potency of dichlorvos as compared to MMS, as noted in the previous section). The mutagenicity seen in micro-organisms is likely to result from DNA methylation.

Dichlorvos has also been shown to produce mitotic gene conversion in the yeast Saccharomyces cerevisiae, this is an 'indicator' of DNA damage which correlates closely with mutagenic events.

Studies to investigate chromosome damage

Conflicting results have been obtained in cytogenetic studies in mammalian cells in vitro. Negative results were obtained in studies using lymphocytes and Chinese hamster V79 cells using high concentrations of dichlorvos (up to about 1m). Positive results were however reported in Chinese hamster lung cells at similar concentrations.

In addition an increase in sister chromatid exchanges has been reported in V-79 cells in vitro, suggesting that dichlorvos can produce DNA damage in mammalian cells.

In vivo studies

Studies in micro-organisms: host-mediated assays

The ability of dichlorvos to produce gene mutation in Salmonella typhimurium, or gene conversion in Saccharomyces cerevisiae, in rodents in vivo has been investigated using host-mediated assays. The 'marker' micro-organisms were given by intra-peritoneal injection and the dichlorvos by various routes (oral, inhalation and sub-cutaneous injection) at high acute dose levels. Negative results were consistently obtained.

Studies to investigate chromosome aberrations

Dichlorvos has been extensively studied for its ability to produce chromosome aberrations in vivo in mice and Chinese hamsters using metaphase analysis of bone marrow cells. Exposure was to high levels of dichlorvos both by inhalation and by the oral route (for example inhalation exposure to 70 mg/m^3 for 16 hours, or 5 mg/m^3 for 21 days, or oral dose of 15 mg/kg). Negative results were consistently obtained.

Dominant lethal assays

Several studies have been reported to investigate the ability of dichlorvos to produce dominant lethal effect in mice. Exposures were again to high dose levels either by inhalation (55 mg/m^3 for 16 hours) or intra-peritoneal injection (16.5 mg/kg). Such treatment of male mice produced no mutagenic effects as expressed by increased pre-implantation losses or early foetal deaths in subsequent matings. In addition no impairment in male fertility was detected.

Thus negative results were consistently obtained in dominant lethal assays in mice.

Summary of mutagenicity of dichlorvos

Dichlorvos has been shown to produce gene mutations in a range of micro-organisms *in vitro*, and there is some evidence that it produces chromosome aberrations *in vitro* although this is conflicting.

However, negative results were obtained in host-mediated assays *in vivo* using strains of *Salmonella typhimurium* and *Saccharomyces ceresvisaie* as marker micro-organisms. The ability of dichlorvos to produce chromosome aberrations *in vivo* has been extensively investigated using metaphase analysis of bone marrow cells; negative results were consistently obtained. The inability of dichlorvos to produce chromosome damage *in vivo* is supported by negative results in dominant lethal assays.

CARCINOGENICITY

National Cancer Institute (US) carcinogenicity bioassays have been carried out using the oral route in both rats and mice.

In mice dietary levels of dichlorvos of about 300 ppm and 600 ppm were given for 78 weeks and the animals observed for a further 12-15 weeks. The only toxic effect seen was a slight reduction in weight gain at the high dose level. No significant difference in tumour incidence were seen in either group of treated animals as compared to the controls.

In the rat study dietary levels of about 150 and 300 ppm were given for 80 weeks and the animals observed for a further 30 weeks. No signs of toxicity were observed in either treated group. The only tumour type that showed any increase in incidence was malignant fibrous histiocytomas in the male rats (2/58 in 'combined' controls compared to 4/48 in low dose and 8/50 in the high dose) but in view of the known variability in the spontaneous incidence of such tumours (the incidence in the 'matched' experimental control was 1/10) and the fact that there was no decrease in time of observation of the first tumour in the treated compared to the control animals, this observation was not considered to have any biological significance.

Thus dichlorvos gave negative results in these dietary carcinogenicity bioassays in rats and mice.

Only one study has been carried out using the inhalation route, but this was not to a scientifically acceptable standard and no conclusions could be drawn regarding the carcinogenicity of dichlorvos. The highest concentration used was only 0.55 ppm, and only one-third of the treated animals were subjected to full necropsy.

Thus the available data from animal studies does not suggest that dichlorvos has any carcinogenic potential.

HUMAN DATA : EXPERIENCE IN USE

No data are available from epidemiology studies to allow any conclusions to be drawn about the mutagenicity or carcinogenicity of dichlorvos in man.

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CONCLUSIONS

Mutagenic risk of dichlorvos to man

Dichlorvos has weak alkylating potential and can methylate DNA. It has been shown to be mutagenic *in vitro* in a range of systems. Most of the data is from bacteria, such as the Salmonella assay, but positive results have also been obtained in assays using yeasts. Chromosome damage has also been produced in mammalian cells *in vitro*.

The alkylating properties of dichlorvos are very quickly destroyed *in vivo*. This is due mainly to rapid metabolism by esterases that are widely distributed in mammals (blood and essentially all tissues). It is exceedingly difficult to actually detect any blood or tissue levels of dichlorvos in animals, with only traces being detected in the kidneys after exposure to high dose levels.

There is convincing evidence that the *in vitro* mutagenicity of dichlorvos cannot be expressed *in vivo* in mammals. Negative results were consistently obtained in bone marrow assays for chromosome damage. Negative results were also obtained in dominant lethal assays, supporting the contention that the compound does not produce chromosome damage in animals. Furthermore negative results were also obtained in host-mediated assays, using bacteria or yeasts as 'marker' micro-organisms.

Animal studies do not indicate that dichlorvos has any carcinogenic potential.

The use of dichlorvos as an insecticide does not present a genotoxic risk to humans.

Testing for Mutagens and Carcinogens: the Role of Short-term Genotoxicity Assays

A Report Prepared by the International Commission for Protection Against Environmental Carcinogens and Mutagens (ICPEMC).

Mutation Res. in press

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SUMMARY

The problems currently besetting approaches to the detection of chemicals likely to pose a mutagenic or carcinogenic hazard to humans are analysed. Some solutions to these problems are offerred.

HISTORICAL CONTEXT

The first practical utilization of mutagenicity data to predict mammalian carcinogenicity was by Boyland. In that case the mutagenicity of nitrogen mustard to Drosophila (Auerbach et al 1943) prompted the prediction and demonstration of its carcinogenicity to mice (Boyland and Horning 1949). The extent and predictive value of the relationship between mammalian mutagenicity* and carcinogenicity has been studied in great detail over the past decade, and although the practicalities of optimally measuring and correlating these two phenomena have advanced (c.f. Montesano et al 1986), it is only recently that the validity of the presumed relationship has been debated. The need for such a debate is illustrated superficially by comparison of the conclusions drawn by Ames and his colleagues (McCann et al) in 1975, with those of Tennant et al in 1987, concerning the value of the Salmonella mutation assay for the prediction of carcinogenicity. McCann et al (1975) concluded that this assay could identify as mutagens ~90% of a group of animal carcinogens,while Zeiger and Tennant (1986) and Tennant et al (1987) concluded the figure to be only about 45% for a different group of carcinogens. This apparent decrease in assay sensitivity was matched by an increase over the same period in the number of non-carcinogens found to be mutagenic to Salmonella in vitro (ie, by a corresponding loss of assay specificity). This trend appears to be in stark contrast to recent progress in cancer research which has been made possible by studies utilizing molecular biological techniques (c.f. Ramel 1986 and Barbacid 1986). Such studies appear to have enhanced the basic premise that mutagenic events play a critical role at several stages of the carcinogenic process.

The sciences of chemical carcinogenicity and chemical mutagenicity remained essentially separate until the early 1970's. The interest shown in both of these topics over the past decade can be traced to three major influences, the inter-relationship between which can account for both the development of this

*Hereafter, mammalian mutagenicity is assumed to imply the induction of either somatic or germ cell mutations in a living mammal. This term includes both gene-mutations and chromosomal aberrations or rearrangements

field, and for the present temporary difficulties. These influences were, first, the heightened general awareness that came about in the late 1960's and early 1970's regarding the possible toxicological impact of increasing exposur of man to synthetic chemicals; second, the formation of the several Environmental Mutagen Societies (EMS); and finally, the assertion made by Ames and his colleagues in 1973 that carcinogens could be detected as mutagens in vitro. Little needs to be said about public and governmental interest in environmental mutagenesis and carcinogenesis apart from commenting that it has stimululated research and assay development, and revealed a number of difficulties inherent in the need to simplify conclusions in order to provide testing framework suitable for incorporation into legislative guidelines and test requirements. A reflection of this influence is provided in the disparat legislative requirements of different countries.

It is interesting that in 1969, at the foundation of the Environmental Mutagen Society (EMS) in the United States, five objectives for the Society were agreed as follows: to encourage interest in mutagens in the environment, to publish a monograph on mutagenicity testing, to publish a Newsletter, to form a registry of chemical mutagens, and to act as a consulting resource to government and industry on such matters. The first official EMS meeting took place a month later, and in the Minutes of that gathering it was suggested that the Newslette should also be circulated to people interested in carcinogenicity, but carcinogenicity figured little in those early meetings.

In the July of 1970, at Munich, Dr Hollaender gave the opening address at the foundation of the European EMS. He restated the Society goal of 'dealing with the factors from our environment which could have a genetic effect'. Only two references were made at that meeting to carcinogenicity, the most pertinent being by Lars Ehrenberg who suggested that in countries with only limited resources, research on carcinogenesis and mutagenesis should be coupled. Likewise, in 1973 the long range planning committee of the United States EMS presented a report which identified nine areas of possible future endeavour for the Society, but the specific study of carcinogenicity, or the evaluation of mutagenicity assays for its prediction, were not mentioned.

In 1973, Ames and his colleagues published a paper which demonstrated that selected carcinogens were mutagenic to Salmonella typhimurium in vitro (Ames et al 1973). Within the next few years the results of several cooperative studies

were presented, and these demonstrated that ~90% of rodent carcinogens were mutagenic to Salmonella while only ~10% of the non-carcinogens evaluated were mutagenic (McCann et al 1975, Sugimura et al 1976). These two papers caught the interest of both the scientific and governmental communities. Asubtle yet ultimately profound effect on mutagenicity research accompanied the widespread adoption of the Salmonella assay - a bacterial mutagenicity assay had been set apart for the prediction of animal carcinogenicity, but the derived mutagenicity data were considered incapable of standing alone as a significant statement of overall mammalian mutagenicity. However, once forged, the empirical correlation between bacterial mutagenicity and mammalian carcinogenicity was accepted, selectively elaborated, and only recently called into question by data such as that of Zeiger and Tennant (1986) and Tennant et al (1987), data which indicated that only about 50% of the NTP carcinogens are mutagenic to Salmonella. The stage was thereby set for a reassessment of some of the underlying assumptions of this science.

DISCUSSION

At the present stage of development of the science some fundamental concepts must replace the present trend to simplification. These are, first, to regard confirmed *in vivo* mammalian mutagenicity as a significant toxicological endpoint in itself, second, to accept the long-established multi-stage nature of carcinogenic processes and to optimize the imperfect but useful relationship between mutagenicity and carcinogenicity, third, to accept that some chemicals affect specifically some stages of carcinogenesis that are independent of mutagenicity, and finally, not to repeat the cycle of the past decade by over-interpreting and simplifying the dramatic and seminal progress currently occurring through molecular biological studies. The most immediately relevant of these are the relationship between mutagenicity and carcinogenicity, and the established complexity of the carcinogenic process itself, and these are discussed next.

The majority of mammalian carcinogens available for study in the early 1970's were by any definition of the term, potent. This was because carcinogenicity bioassays conducted before that time were usually of limited statistical resolving power and of short duration. In contrast, the chemicals evaluated for mutagenicity *in vitro* by Tennant et al (1987) included many weak and species-specific carcinogens which would not have been detected using the cancer

bioassay protocols current in the early 1970's. This could provide one possibl key to the disparity in the conclusions derived by these two groups. This is not to imply that only potent carcinogens are mutagenic, but rather, that lifetime administration of a non DNA-reactive chemical to animals may lead to a increase in tumour incidence in certain tissues as the result of non-genetic effects. Such chemical disturbance of normal body homeostasis could be highly specific in terms of the species, strain, sex or tissues affected. This suggestion is not novel. For example, Malling and Chu (1974), in an early pape dealing with the development of mutation assays for the study of carcinogenesis, stated that the correlation between carcinogenicity and mutagenicity cannot be expected to be complete because carcinogenic hormones may not be mutagenic, promotors that may change the intracellular or extracellular conditions permitting pre-neoplastic cells to develop into tumors may not be mutagenic, etc. Clayson (1987) has attempted to define some of the mechanistic factors responsible for the existence of these presumed non-genotoxic carcinogens. He has suggested that the present confusion arises largely from an inadequate operational definition of the term carcinogen - 'an agent which increases the rate of formation of tumours in a population'. This definition includes both those agents that initiate as well as those that merely enhance carcinogenesis. Thus, Clayson argues that the presence of a significant background of tumours in untreated animals, as for example with liver tumours in B6C3F1 mice, greatly increases the possibility for the classification of a tumour enhancing agent as a carcinogen. Furthermore, high dose toxicity due to inappropriate dose selection may lead to both genomal changes and the induction of processes such as cellular proliferation that may enhance carcinogenesis. These and other considerations indicate that properties of a chemical other than mutagenicity may play a critical role in the expression of tumours during its bioassay for carcinogenicity. Further, it follows that these non-genetic effects may of themselves lead to tissue-specific carcinogenic responses for certain non-mutagens in some species or strains of animal.

Underlying mechanisms and the correlation between mutagenicity and carcinogenicity can now be quantitatively as well as qualitatively investigated using the wealth of data which has accrued over the past decade, and it is suggested here that this represents the single most important current need of the science. The simplistic assumption that all chemical carcinogens will prove to be mutagenic <u>in vitro</u>, if tested to exhaustion, will probably prove to be as unrewarding and potentially damaging to the science as would be the rejection of a useful correlation between mutagenicity and carcinogenicity.

The Commission therefore proposes the need for two complementary lines of enquiry and experimentation. First, to consider how most effectively and efficiently to identify mammalian mutagens, an endeavour which should include consideration of the difference between effects seen in vitro and in vivo, and which should take account of genotoxic phenomena ocurring in vivo, but which cannot be described accurately as mutagenic events. Second, to re-evaluate which of the several stages in the carcinogenic process genotoxicity data are most relevant to, and thereby to indicate where supplementary assays that measure relevant biological changes in a tissue may be required to produce more refined predictions of mammalian carcinogenicity. Within that context the following developing principles of genetic toxicology are suggested for consideration:

1. Knowledge of the ability of a substance to induce mutations in the whole mammal provides essential toxicological information, irrespective of a correlation between mutagenicity and carcinogenicity. Agreement should therefore be sought regarding the selection and conduct of a minimal but sufficient number of in vitro assays for prescreening for agents likely to be mutagenic to either the somatic or germ cells of mammals. Although the number of established germ cell mutagens is not large, most of them can be detected with a small number of in vitro prescreen tests, perhaps as few as two. The same is very largely true for whole mammal somatic cell mutagens, of which there are many more. It should be acknowledged that for mutagenicity prescreening purposes there is currently high redundancy among in vitro assays and they tend to have a low specificity, i.e., they identify a substantial proportion of agents as in vitro mutagens that do not possess significant activity in vivo. Not withstanding, the general accessibility and practical facility of the Salmonella assay suggest that it should form a primary component of a prescreen. To complement it, a mammalian cell assay is regarded as derirable, and an assay for the induction of chromosomal aberration in vitro has advantages over other possible candidates as it is widely used, utilizes a particularly relevant endpoint and there is a growing appreciation of its limitations and possible artefacts (Scott 1986, Brusick, 1987). Other established in vitro assays have value in the study of mechanistic aspects of mutagenicity, but there is little evidence at present to suggest that their

use either in addition to or in place of the above tests would make prescreening significantly more effective. The criteria for acceptability of mutagenicity data should be the biological validity of the assay system, the integrity of the protocol employed, the reproducibility of the effect observed, and the degree of specificity with which the genetic parameter under study may be measured.

It must be emphasized at this point that recent evidence from studies measuring the activation or mutation of cellular and viral oncogenes indicates that genetic changes in tumourogenicity may comprise a wider spectrum of DNA alterations than are currently measured by standard mutagenicity assays. Thus, effects on proteins, gene amplification, insertion mutations, hypomethylation of cytosine residues, and to some extent recombination events, may in future become important components of an efficient prescreen for the detection of carcinogens. However, this should not be assumed in the absence of data.

2. Most chemical mutagens require metabolic conversion to an electrophilic/radical species. In in vitro test systems this may take place to some extent within the marker organism, but it is general to rely on a source of exogenous enzymes, usually derived from induced rat liver and supplemented by co-factors (S9 mix). Differences in auxiliary metabolism (S9 mix) is probably the major determinant of differential mutagenicity of a chemical between different in vitro assay systems. This suggests that the interpretation of mutagenicity data derived from several assays would be facilitated by initially reducing the number of assay cell lines, by standardising the S9 mix and by determining different mutagenic events under the same conditions of test (e.g. in the same cell line). From this standardised database further useful information may be gathered by varying the S9 mix, or its conditions of use, in a planned manner. At present, these variables tend to be changed haphazardly between assays. In particular, conclusions of genetic specificity of mutagenic action for a chemical should be drawn only when the possible role of competing metabolic variables have been eliminated. The general failure to heed this precaution underlies much of the present confusion in mutagenicity test battery design - a range of genetic endpoints are ostensibly selected, but the primary variable in reality is usually the range of different metabolic environments offered to the chemical by the different assays. Consequently, it may be more profitable to concentrate on a small number of

assays (of adequate statistical power) and to increase the number of metabolic activation conditions employed. The uniform activity of direct acting mutagens such as EMS in all assay systems supports this suggestion. Techniques are currently available, or are under development, to study the extent of DNA interactions, for example, by the identification, quantitation and repair of DNA lesions (among them DNA adducts). Moreover, recombinant DNA techniques will soon allow the detection of mutations at the molecular level (Lohman et al, 1987). Such procedures, though costly in time and resources, would enable quantitative comparisons between different test systems, and from this it may be possible to define a genuine and agreed example of a chemical with true genetic specificity of mutagenic action.

3. Within the context of mammalian mutagenicity, greater weight should be afforded to those mutagens which are active in the whole mammal as opposed to those which are mutagenic only in vitro [c.f. 7 below]. The failure of an in vitro mutagen to be absorbed in vivo, or its preferential detoxification in vivo, could account for the latter activity profile. A growing body of evidence also indicates a further hierarchy of activities, namely, that the ~40 established rodent germ cell mutagens are also rodent somatic cell mutagens, in particular, to the bone marrow (Holden 1982). The implication of this is that an in vitro mutagen found to be non-mutagenic to somatic tissue will not pose a mutagenic hazard to the germ cells. Further studies to evaluate the generality of this observation are to be encouraged as it presents a powerful aid to relative risk assessment.

4. The experimental conditions under which chemical mutagenicity is established influences its toxicological significance. Thus, a chemical which is mutagenic to the somatic and/or germ cells of a rodent following its exposure to non-lethal dose levels via a natural route of exposure must be considered a greater potential human hazard than one whose mutagenicity can be demonstrated only under extreme conditions of test in vitro (eg, high dose levels which modify the osmolarity/pH etc, of the assay medium). Such considerations must form a critical component of any mutagenic hazard assessment process. At the extreme is the prospect that some mutagenicity data are of no biological relevance because they are observed only under such extreme conditions of test that the integrity of the assay is called into question. Such practical restraints on data generation and interpretation should apply to both in vitro and in vivo mutagenicity

assays, although most data to support this general concern are currently available only for *in vitro* assays (Scott, 1986, Brusick, 1987). The generation of potentially artefactual data usually derives either from inadequate assay protocol design, or continued attempts to elicit a mutagenic response from an apparently non-mutagenic carcinogen.

5. Despite the fact that not all *in vitro* mutagens prove carcinogenic, and that not all rodent carcinogens are mutagens, a strong and growing body of evidence associates these phenomena. It is therefore concluded that the most efficient way in which to commence the evaluation of an agent for genotoxic carcinogenicity is to determine its status as a mutagen. As discussed above, this may be achieved using a small number of established and reliable *in vitro* mutagenicity assays. Early expectations that all carcinogens would be mutagenic led to the development of a large number of additional *in vitro* assays designed with the hope of detecting as positive those carcinogens found to be inactive in the standard mutagenicity tests. Unfortunately, these assays have, by and large, detected the same group of mutagenic carcinogens, a fact which has contributed to the considerable redundancy among *in vitro* assays. Some of these assays monitor cellular modifications which cannot be classed strictly as mutagenic events, and this has necessitated use of the phrase 'genotoxicity assay'. However, if the reality of non-mutagenic carcinogens as a class is accepted (see 8, below) then the deployment of these additional *in vitro* genotoxicity assays to detect them has no rational basis. Nonetheless, the measurement of these endpoints *in vivo* may have a useful role to play in hazard assessment studies.

6. Some genotoxicity assays in current use have been inadequately developed. This is a source of concern on three levels. First, until an assay has been in use for a sufficient period of time, and in several laboratories, it is not possible to assess its sources of intrinsic variability. As a consequence, test criteria will remain insecure, and this may lead to qualitative differences in test responses to the same chemical when tested in the same assay, but in different laboratories. Second, if an assay is employed before its protocol has been adequately defined, discordant results from different laboratories may be generated. This problem was

encountered in the recent IPCS study (Ashby and de Serres et al 1985) where, for example, major uncertainty was encountered regarding the optimum selection and conduct of mammalian cell gene mutation assays. Finally, the true value of an assay is seldom established before it is adopted for routine use, mainly because only a few potent carcinogens/bacterial mutagens are employed during its 'validation'. Thus, the EMIC file reveals that by April of 1986, more than 20,000 chemicals had been evaluated for genotoxicity, and in excess of 10,000 of these had been evaluated in a single test, and only once. In contrast, of the 62,500 literature references in the file, 4094 referred to the activity of EMS, 4076 to that of MNNG, 2188 to BP, 1995 to MMS and 1757 to MNU, etc. It is virtually impossible to assess the strengths and weaknesses of an assay using such agents - that usually awaits their premature use to evaluate new chemicals, but at that stage positive test criteria have to be developed around the equivocal test data which are inevitably produced. Such factors make it very difficult to use published genotoxicity data to derive empirical correlations with carcinogenicity or to provide evidence for test battery design.

7. Recent data derived by the US National Toxicology Program (NTP) establishes unequivocally that not all in vitro mutagens prove to be carcinogenic to rodents (Shelby and Stasiewicz 1984, Zeiger and Tennant 1986, Tennant et al 1987). Consequently, mutagenicity data derived from experiments conducted in vitro only provide an alert to potential carcinogenicity. They are not a substitute for carcinogenicity bioassays. The unexpectedly high incidence of mutagenic non-carcinogens indicates that a method of qualifying in vitro mutagenicity data must be sought. It seems probable that the pharmacokinetic/metabolic factors which prevent some in vitro mutagens from eliciting mutations in vivo may also be responsible for the absence of induction of cancer for some in vitro mutagens. If this is so, then the observation of mutagenicity in vivo for a new in vitro mutagen increases greatly the probability that it will also prove carcinogenic. This use of in vivo genotoxicity data may provide a solution to the problem of qualifying in vitro mutagenicity data when using it to predict genotoxic carcinogenicity. Thus, a new in vitro mutagen which is non-genotoxic in vivo may be concluded to have a lowprobability of being a genotoxic carcinogen as compared to one which is active in vivo. This approach could be enhanced by consideration of effective dose-levels and dose response effects in vivo (Clayson, 1987). Sole reliance on negative mutagenicity

data derived from the rodent bone marrow is not recommended as several clearly mutagenic (in vivo) carcinogens are inactive in this tissue. This has led to the suggestion that mutagenicity/genotoxicity data from at least two rodent tissues should be employed for such hazard assessment studies (Ashby 1986). By segregating mutagenicity and carcinogenicity dat as overlapping toxicological phenomena of independent significance it is possible to avoid use of the phrase 'false positive results'. This phras should be restricted to mutagenic events monitored in vitro and which are established as artefacts of inadequate test protocols (c.f. Brusick 1987) Thus, by studying mutagenicity in vitro and in vivo it is possible to derive a more complete measure of the mutagenicity of a chemical. The mo refined that knowledge is, the more refined can be the derived estimate o an agents' potential in vivo mutagenicity or genotoxic carcinogenicity. Attempts made over the past decade to simplify the relationship between mutagenicity and carcinogenicity by use of the term 'false positive' have led to unnecessary confusion. Thus, positive Salmonella mutagenicity dat derived for a non-carcinogen are generally referred to as being false, yet the inactivity of the same agent as a clastogen to the rodent bone marrow would normally be attributed to the relative insensitivity of the in vivo mutagenicity assay - this exemplifies the results of an over-simplification of complex biological phenomena.

In cases where mutagenic changes cannot be directly measured in a tissue, use of non-specific genotoxicity assays is indicated. These could include DNA binding studies or the post-labelling assay described by Randerath et al (1981) and Gupta (1985). The latter techniques may also play a useful role in studying site-specific initiation, especially as it may relate to organotropic carcinogenic responses.

8. While the majority of rodent carcinogens defined to date are also mutagens, some appear to have a chemical structure devoid of actual or potential electrophilic centres, and to be non-mutagenic. This suggests that some chemical carcinogens do not possess initiating action but are able to cause the development of tumours by modification of the environmer of certain rodent tissues such that pre-initiated cells can develop into tumours. Pre-initiated cells may arise through unmonitored exposure to initiating agents in the test environment, or they may arise as the consequence of unknown processes. Use of words such as promoting agent,

epigenetic carcinogen, etc, to describe these agents does little beyond providing a name for little understood phenomena. Standard mutagenicity assays will not alert to them, thus their detection must be based on assays which monitor changes in either cellular control mechanisms or cellular environments (eg, Yamasaki, 1987). Modulation of either the hormone status of an animal or of the mitotic activity of certain of its tissues following exposure to a non-mutagen has been suggested by several investigators to provide evidence of a possible non-mutagenic carcinogen. Such biological data are often accessible fromother experimental studies, especially with agents of environmental importance. But it would be unwise to reduce this problem into a set of empirical assays for non-genotoxic carcinogens before adequate understanding of the underlying causal mechanisms is available (Douglas et al, 1987).

The direct modification of the cellular genome by genotoxic carcinogens provides an appealing explanation for why tumours can develop after a latency period following the cessation of dosing with the carcinogen. In contrast, the development of tumours by exposure to a non-mutagenic carcinogen may be dependent on chronic administration of the chemical in order to maintain an altered expression of the genome, leading eventually to tumours. The latter requirement is most adequately fulfilled by the life-time exposure carcinogenicity bioassays employed by the NTP. Thus, the effect of reducing the period of exposure to a non-mutagenic carcinogen may be to abolish its carcinogenicity, and were this to be established it would have a profound influence on subsequent human risk estimations. Similarly, it is possible to consider that non-genotoxic carcinogens may have a threshold dose below which they are non-carcinogenic, but this cannot be assumed in the absence of supporting data. Further, although itis usually observed that comparatively high exposure levels are required to demonstrate carcinogenicity for a non-mutagen, compounds resistant to biodegradation and/or subject to bioaccumulation may produce effects at very low dose-levels [e.g. 2,3,7,8-tetrachlorodibenzodioxin (TCDD)].

Dose-response relationships in chemical carcinogenesis are clearly of profound importance. This is because they may differ between different mechanisms of tumour induction, and because most carcinogenicity data are generated at dose-levels much higher than those expected to occur under normal conditions of human exposure (discussed further by Clayson, 1987).

Strong evidence that there may be two classes of chemical carcinogen, genotoxic and putatively non-genotoxic, was provided by the results of a study recently reported by Ashby and Tennant (1987). This emerged from a detailed analysis of 222 chemicals that had been evaluated by the US NTP for carcinogenicity in adequate lifetime studies, using B6C3F1 mice and F344 rats. The 115 carcinogens considered were separated into 70 which induced tumours at multiple sites, and/or in both species, and 45 which were only active at a single site in a single species. Equivocal evidence of carcinogenicity had been recorded for a further 24 chemicals, and 83 chemicals were reported as non-carcinogenic. Structural analysis of these 222 agents was then undertaken according to the electrophilic theory of carcinogenesis (Miller and Miller, 1977, as summarised by Ashby 1985), and these data were compared with the level of carcinogenicity of the agents and with their mutagenicity to Salmonella. The results established a high concordance between structural alerts to carcinogenicity and mutagenicity to Salmonella for all of the agents (~90%). This suggests that the Salmonella assay is an efficient detector of intrinsically genotoxic chemical moities. Moreover, the group of multiple site/trans-species carcinogens contained a much higher proportion of mutagens (70%) than did the group of single-species/single-site carcinogens (39%). In fact, the incidence of mutagens in the latter group of carcinogens was similar to that observed for the equivocal carcinogens and for the non-carcinogens (~30%). These data therefore provide strong inferential evidence that the 45 'selective' carcinogens (~40% of the 115 NTP carcinogens considered) were increasing the tumour incidence in the treated animals by mechanisms unlikely to require or involve their primary covalent interaction with DNA. In contrast, by regarding all of the NTP carcinogens as equivalent in terms of their mechanism of carcinogenic action one can account for the low overall sensitivity figure of 45% recorded recently by Tennant et al (1987) for the Salmonella assay.

In summary, the adequate evaluation of a chemical for mutagenicity in vitro provides a sentinel observation for predicting potential genotoxic carcinogenicity; but not all rodent carcinogens are genotoxic. It is therefore suggested that the relevant question is how non-genotoxic carcinogens act and may be predicted, rather than whether they exist.

9. Molecular biological techniques are rapidly expanding our understanding of chemically-induced cancer, and they have the potential to be modified for use in hazard assessment studies. However, they may be difficult to develop for routine use as an adjunct, for example, to standard *in vitro* assays. Such practical considerations apart, a more fundamental question is posed by consideration of such techniques. This is exemplified by the model experiments described by Marshall et al (1984). These authors described the chemical mutation *in vitro* of cloned Harvey ras proto-oncogenes, followed by their transfection into cultured 3T3 cells, thereby leading to cell transformation *in vitro*. The authors employed the ultimate electrophilic species derived from benzo[a]pyrene for these studies, an agent which is a potent mutagen in all standard mutagenicity assays. However, were this to be used as an *in vitro* assay for oncogene mutation it would be equally prone to the problems common to all *in vitro* assays, i.e. it would almost certainly generate positive responses for non-carcinogenic Salmonella mutagens such as those described by Shelby and Strasiewicz (1984). Equally, such an assay would be subject to the problems imposed by the use of S9 mix, and the non-mutagenic carcinogens discussed above (section 8) would probably remain undetected. Thus, once a chemical can be established as mutagenic *in vitro* it will probably be equally as effective at reverting the *his* gene in Salmonella as it is at mutating cloned H-ras genes *in vitro*. However, the development of anassay for oncogene mutations in rodents would hold great promise.

In summary, the use of molecular biological techniques may, at least initially, be limited by the availability of the required expertise, and perhaps by their cost, but if developed mindful of the real current problems of carcinogen prediction, valuable and practical *in vivo* assays will evolve. Reynolds et al (1987) have recently suggested that the pattern of oncogene mutation (activation) in B6C3F1 mouse liver tumours may lead to the separate identification of spontaneous and chemically-induced tumours, ie, molecular biological techniques may offer a method of distinguishing genotoxic from non-genotoxic carcinogens.

It is worth noting that many recent studies on the molecular biology of cancer have employed induced cell transformation *in vitro* as a surrogate for the tumourogenic state when monitoring the mutagenic activation of

proto-oncogenes. However, a large body of evidence supports the fact that *in vitro* cell transformation assays are not practical or reliable enough for routine screening use (*inte alia*, Ashby and de Serres et al., 1985). Thus, although these assays may continue to provide a valuable technique in carcinogenesis research, they remain unsuitable for routine deployment.

10. It is suggested that the most important present need of this field is to desist from seeking a simple solution for the problem of chemically-induce cancer. Rather, mutagenicity data should be accepted both as an importan toxicological endpoint in their own right, and as a critical contributory factor in genotoxic carcinogenesis. Mutagenicity data should therefore form a critical component of the overall toxicological assessment of a chemical. Further, when integrated with other toxicological data they can provide a refined estimate of an agents' potential carcinogenicity.

Non-genetic biological effects of a chemical may play a critical role in the clonal propogation of a mutated cell into a tumour, and such species/sex/tissue-specific activities may correlate with the species/sex/tissue-specificity of an agent as a carcinogen. Thus, when both mutagenicity and 'toxicity' occur with the same chemical in the same tissue, it is suggested that the probability of observing tumours in that tissue may be increased (Bernstein et al 1985). This assumes that a mutagen has the potential to act as an initiating agent in many tissues of a rodent, yet tumours may develop only in those in which it also exerts a (perhaps subtle) non-genetic activity. Such activities may vary between tissues as the dose-level of the chemical is altered, and this may explain changes in carcinogen organotropy with changes in dose-level (Schmahl, 1981). The importance of such multifactorial influences on carcinogenesis is well established for the rodent liver (Pitot and Sirica 1980; Tsuda et al 1980) and bladder (Clayson 1981), but they are generally incapable of simulation in cultured cells, and are therefore usually incapable of prediction *in vitro*. It must be accepted that while it may be possible to expose rodents to a sufficient dose-level of an agent to elicit non-genetic secondary effects, such may not occur in human exposed to lower dose-levels. Thus, caution is required when extrapolating rodent carcinogenicity data to humans.

In summary, the Commission suggests that the potential mutagenicity of a chemical for the somatic or germ cells of humans can be predicted using currently available techniques and with a level of certainty proportional to the quality of the toxicology, genetics and thought devoted to the task. Second, that mutagens, particularly those active in the whole mammal, may be regarded as potential genotoxic carcinogens. Third, that the non-genetic effects of a chemical may play a critical role in the development of appropriately mutated cells into tumours, and of producing selective carcinogenic effects in some species or strains of rodents chronically exposed to the agent. Finally, that molecular biological techniques hold great promise for the future of this science. These considerations indicate that the study of environmental mutagens and carcinogens can best be approached via the integrated and quantitative assessment of the toxicology of a chemical - there are no simple solutions, equally, current problems are not insoluble. Dramatic progress has been made over the last decade, and the time to re-focus research and attitudes has arrived.

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7/2 87

P. Corcoran

Potentially Toxic Chemicals

Pesticides — MAFF agricultural
— HSE non agricultural

Pharmaceuticals — DHSS human health
— Environment ?

Food additives } MAFF agriculture
veterinary products } DOE Environment.

Individual chemicals : existing — AD Hoc — HS
— PCB
— PDT
— Pesticides.
— Systematic — have to choose chem
what information
- testing
- monitoring
impact
how to choose between
diff. testing
(national
organisation)

: new chemicals - HSE
- DOE

CPL / Transport

education skill

access existing
chemicals

PLs (not toxic chem.)

Basis : — guide notification chemical recognition
— channel with control — new chem. testing
technology.

target : chemical chemistries

inhalation /
skin rashes.
irritation.

chem ? — where come from
— where to go
— what happens if we realise goes
what in the end it would be.

Environmental Control

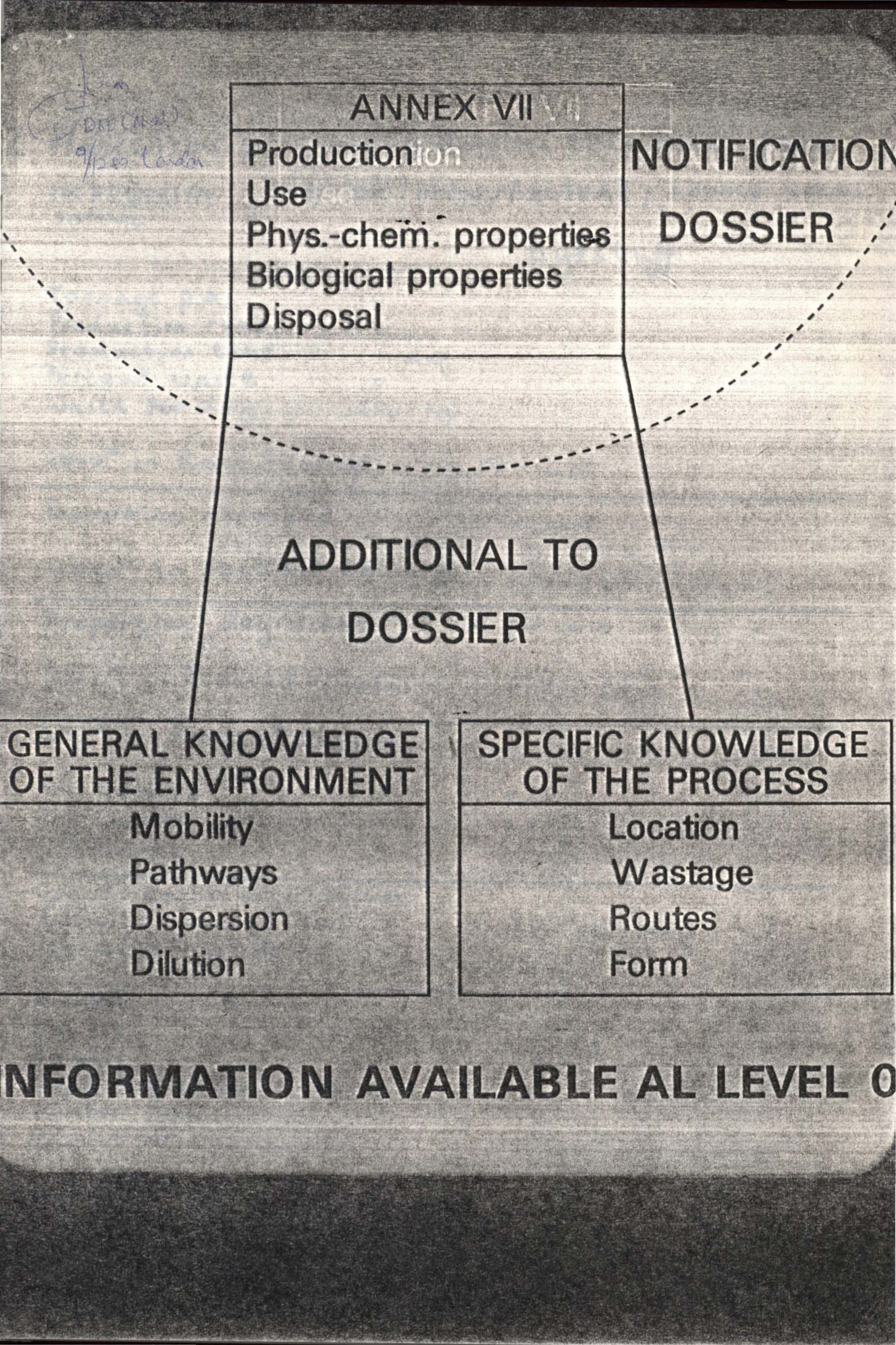
air — fixed sources
— mobile "

water — emissions
— EQO / EQS

Wastes — controlled
— special.

Pharmaceuticals / toxic

monitoring


ANNEX VII
Production
Use
Phys.-chem. properties
Biological properties
Disposal
NOTIFICATION
DOSSIER
ADDITIONAL TO
DOSSIER
GENERAL KNOWLEDGE
OF THE ENVIRONMENT
Mobility
Pathways
Dispersion
Dilution
SPECIFIC KNOWLEDGE
OF THE PROCESS
Location
Wastage
Routes
Form
NFORMATION AVAILABLE AL LEVEL 0

2. PREDICTION OF CONCENTRATION RESULTING FROM INDUSTRIAL USE OR MANUFACTURE; SEWAGE WORKS DISPOSAL

Dyestuff

Tonnage p.a.	10	
Production runs	4	
Production time	1 day	
Percent waste	10	
Waste per day	250 kg	
Conc^n in Raw Sewage	104.17	$mg\,l^{-1}$
Proportion absorbed	99	per cent
Conc^n in Settled Sewage	1.04	$mg\,l^{-1}$
Proportion degraded	0	per cent
Conc^n in Treated Effluent	1.04	$mg\,l^{-1}$
Conc^n in Rivers at Outfall		
0.1 Cumec	0.23	
0.5 Cumec	0.055	$mg\,l^{-1}$
1.0 Cumec	0.048	
Conc^n on Sewage Solids Assuming sewage is 330 $mg\,l^{-1}$ solids	31	per cent
Arable Land		
Density	1.5	$g\,cm^{-3}$
Depth	20	cm
Total Dry Solids p.a.	2	tonnes $hectare^{-1}$
Number applications	1	
Amount per application	6.25×10^8	mg $hectare^{-1}$
Soil conc^n per application	208.33	$mg\,kg^{-1}$

PHYSICO CHEMICAL PROPERTIES REQUIRED FOR LEVEL 0

Melting Point

Boiling Point

Relative Density

*Vapour Pressure

Surface Tension

*Water Solubility

*Fat Solubility

*Partition Coefficient (n-octanol/water)

Flash Point

Flammability

Explosive Properties

Auto-flammability

Oxidising Properties

INFORMATION REQUIRED IN A TECHNICAL DOSSIER FOR A FULL NOTIFICATION

Notifier's Name — **manufacturer or importer**

Substance
- **identity**
- **quantity**
- **use**
- **distribution**
- **method(s) of detection and determination**
- **physico chemical properties**
- **mammalian toxicity**
- **ecotoxicity**

Recommendations for
- **safe handling**
- **disposal**
- **classification**
- **labelling**

(based on mammalian toxicity)

Notifier's own assessment of the potential hazard

ECOTOXICITY TEST RESULTS REQUIRED FOR LEVEL 0

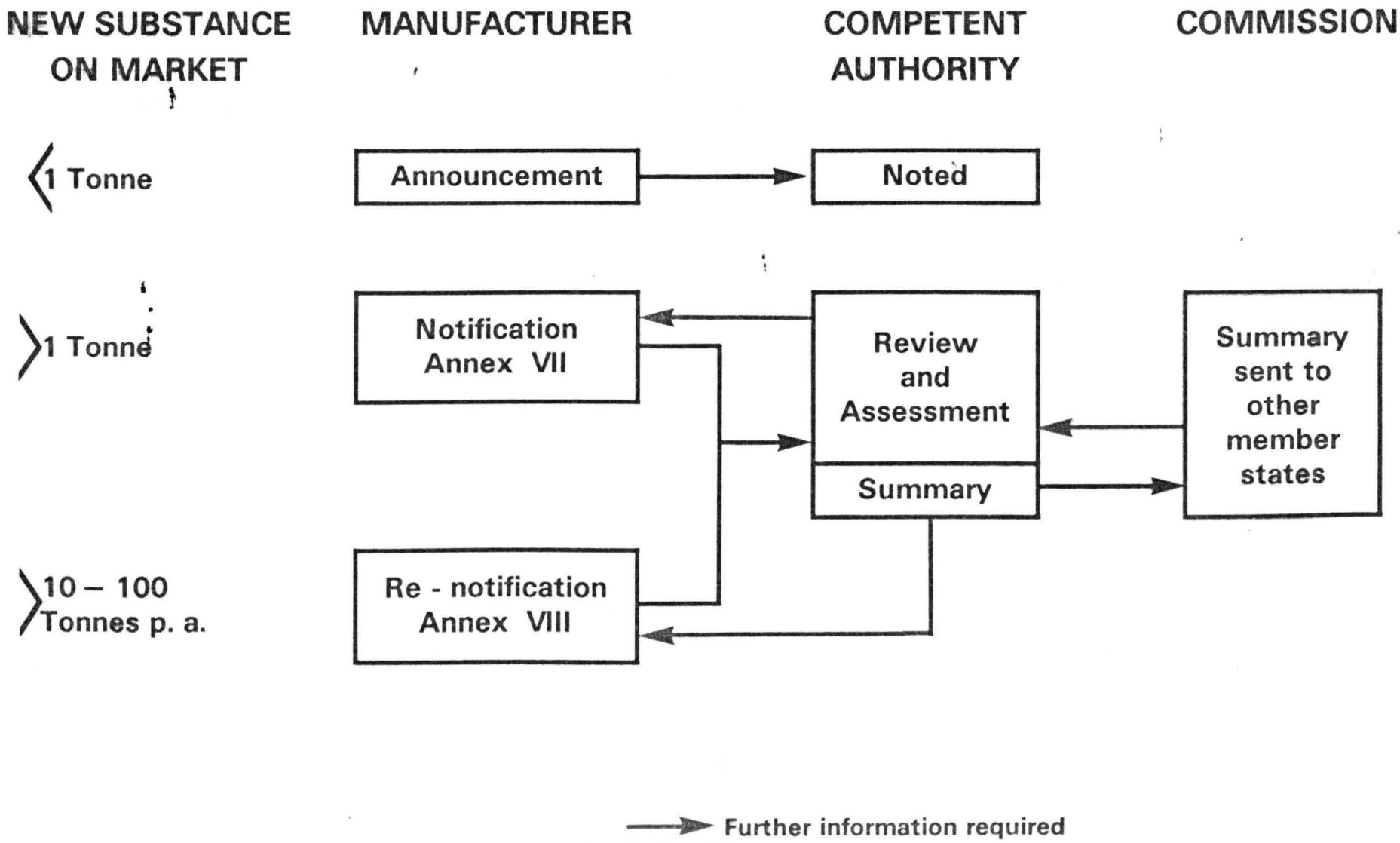
Acute Toxicity	—	**fish**
	—	**Daphnia**
Degradation, biotic		
Degradation	—	**biochemical oxygen demand**
	—	**chemical oxygen demand**
Degradation, abiotic	—	**hydrolysis as a function of pH**

3 PREDICTION OF ENVIRONMENTAL CONCENTRATION RESULTING FROM WIDESPREAD USE

Linear Alkylbenzenesulphonates

Tonnage p.a.	70 000	
Days of use	365	
Percentage waste	100	
Sewage Volume	1.3×10^{10}	$m^3\ day^{-1}$
Concentration in Raw Sewage	14.53	$mg\ l^{-1}$
Percent Absorbed	30	
Conc^n in Settled Sewage	10.17	$mg\ l^{-1}$
Percent Degraded	70	
Conc^n in Treated Effluent	3.05	$mg\ l^{-1}$
Conc^n in Rivers at Outfall		
0.1 Cumec	0.674	$mg\ l^{-1}$
0.5 Cumec	0.161	
1.0 Cumec	0.082	
Conc^n on Sewage Solids (330 $mg\ l^{-1}$ solids)	1.32	per cent
Arable Land		
Density	1.5	gcm^{-3}
Depth	20	
Total Dry Solids p.a	5	tonnes hectare^{-1}
Number of Applications	3	
Amount per Application	7.42×10^6	mg hectare^{-1}
Soil conc^n per application	7.04	$mg\ kg^{-1}$

NEW CHEMICALS NOTIFICATION SCHEME



EXAMPLES OF NOTIFIABLE CHEMICALS

dhesives

ntioxidants

apacitor fluids

atalysts

orrosion inhibitors

etergents

isinfectants

illing fluids

yes

rtilisers

ame retardants

Inks

Leather processing chemicals

Lubricants

Paints

Paper manufacturing chemicals

Photographic chemicals

Plasticisers

Solders/fluxes

Solvents

Textile manufacturing chemicals

Welding aids

INFORMATION ON ROUTES OF EXPOSURE TO THE AQUATIC ENVIRONMENT

from: River Pollution Survey of England and Wales, updated 1975. River Quality and Discharges of Sewage and Industrial Effluent

1 INDUSTRIAL PROCESS WATER DISCHARGES

- use mean volume per day for the relevant industry

2 SEWAGE WORKS CAPACITY

- use 'typical' works serving 10000 people

Dry weather flow of waste water per head per day	240 litres
Made up of - Domestic	180 Litres
- Industry	60 Litres
Total Sewage volume per day	2400 m^3
Solids production for 10000 population per day	800 kg

NA 2

1 PREDICTION OF CONCENTRATION OF A SUBSTANCE DIRECTLY DISCHARGED DURING MANUFACTURE OR USE

Plastic Precursor

Tonnage per annum	55	
Production Runs	10	
Production Time	5	days
Percent Waste	0.05	
Waste per day	0.5	kg
Industry process water output	287	$m^3\ day^{-1}$
Concentration in output	1.92	$mg\ l^{-1}$
Concentration in:		
0.1 Cumec	0.063	
0.5 Cumec	0.013	$mg\ l^{-1}$
1.0 Cumec	0.006	
rivers		

3 RIVER FLOW RATES

- use 0.1, 0.5 or 1.0 cubic metres per second

from: Water Directorate, DoE

4 SLUDGE APPLICATION RATES

- use different sets of data for Grazing and Arable land

Arable Land
- up to 5 tonnes of dry solids per hectare per year
- soil depth 20 cm
- up to 6 applications
- soil density 1.5 g cm^{-3}

Grazing Land
- up to 3 tonnes of dry solids per hectare per year
- fewer applications
- soil depth 7.5 cm
- soil density 1.5 g cm^{-3}

EXPOSURE ASSESSMENT

1 Assume all waste goes to the aquatic environment.

unless
- very toxic to rats and use suggests leaching from landfill
- high tonnage substance with very high vapour pressure and very toxic by inhalation

---

INITIAL ASSESSMENT OF AQUATIC EXPOSURE - ROUTES TO THE ENVIRONMENT:

1 Direct Discharge of Waste into Rivers

2 Disposal via Sewage Works

3 Disposal via Sewage Sludge to Land

ECOTOXICITY TEST RESULTS REQUIRED FOR LEVEL 1

Toxicity	—	algae
	—	higher plant
	—	earthworm
Prolonged Toxicity	—	fish
		Daphnia
Bioaccumulation	—	one species (preferrably fish)
Biodegradation	—	prolonged, if not proven at Level 0

ECOTOXICITY TEST RESULTS REQUIRED FOR LEVEL 2

Additional tests	—	accumulation
showing effect on	—	degradation
food chain	—	mobility
Prolonged toxicity	—	fish reproduction
Acute and Sub–Acute Toxicity	—	Birds (if accumulation factor > 100)
Additional Toxicity	—	as required
Adsorption – Desorption	—	if substance not degradable

TOXICITY TEST RESULTS REQUIRED FOR LEVEL 0

Acute Toxicity	—	**oral**
	—	**inhalation**
	—	**dermal**
	—	**skin irritation**
	—	**eye irritation**
	—	**skin sensitization**
Sub–acute Toxicity	—	**oral**
	—	**inhalation**
	—	**dermal**
Mutagenicity	—	**one bacterial**
	—	**one mammalian**

S/1? Brooke

DR D N BROOKE

S/2

ENVIRONMENTAL ASSESSMENT OF NEW CHEMICALS IN THE UK

A Exposure Estimation

1 Type of method.

The method is based on the development of appropriate scenarios for each chemical to estimate the discharge to the aquatic (and terrestrial) environments.

2 Purpose/scope of estimation

The purpose of this approach is to estimate the concentration of the chemical at the point where it enters the aquatic and/or terrestrial environment. It may be applied at three points in the life-cycle of the chemical: manufacture, use and disposal. The initial data available for a new chemical are usually sufficient to enable a screening estimation to be made of likely environmental concentration. Further information may become available at higher tonnages to allow the assessment to be refined. The method is applicable to chemicals which are considered or known to be transported to the environment either in solution or suspension and also as a solid in waste.

3 Description of the method

The method is based on the development of the relevant scenarios, and is performed by making a series of simple calculations as illustrated below. The individual equations are applicable for both low and high tonnages. The data available and any assumptions which need to be made are used to create "worst case" situations.

3.1 Manufacturing stage.

Let Q = production quantity per annum

W = wastage as percentage of production

N = number of batches produced per annum

S = number of manufacturing sites

then B = quantity per batch per site = $\frac{Q}{NS}$

and B_W = waste per batch = $\frac{Q}{NS} \cdot \frac{W}{100}$

If V = volume of effluent from the manufacturing site, then the concentration of the chemical in the effluent from the site, C_E, is given by

$$C_E = \frac{B_W}{V}$$

Discharge options.

A: Direct to surface water.

The concentration in surface water will be affected by the dilution of the effluent stream in the river. For a dilution D_{SW}, the concentration below the discharge (C_{SW}) will be

$$C_{SW} = C_E . D_{SW}$$

The dilution is given by

$$D_{SW} = \frac{V}{V+V_R}$$

V = volume of discharge, m^3/day

V_R = river flow upstream of discharge, m^3/day

B: To surface water via treatment plant

There are three ways in which the concentration of the chemical can be reduced by passage through the sewage treatment works (STW).

i Dilution before reaching STW (ie in the rest of the inflow to the works)

As above, if the dilution is D_T, then the concentration on entering the works is C_T:

$$C_T = C_E . D_T$$

The dilution $D_T = \frac{V}{V_T}$ where V is the volume of discharge, m^3/day

V_T is total inflow into STW m^3/day (this includes V).

ii Absorption on to solids.

If A% of the chemical is absorbed by solids, then the concentration remaining in the liquid phase, C_L is

$$C_L = \frac{100-A}{100} . C_T$$

If S is the amount of solids removed (dry weight) per day, and the volume of waste from the manufacturing site per day is V, then the concentration in the solid phase, C_S is

$$C_S = \frac{\Lambda}{100} \cdot \frac{C_E.V}{S}$$

iii Degradation on treatment.

If E% of the chemical is eliminated during treatment, then the residual chemical concentration to be discharged, C_R, will be

$$C_R = \frac{100-E}{100} \cdot C_T \qquad \text{for no absorption}$$

$$= \frac{100-E}{100} \cdot C_L \qquad \text{for absorption}$$

Finally, there will be further dilution when the STW discharge reaches surface water:

$$C_{SW} = C_L \, D_{SW}$$

where $D_{SW} = \frac{V_{STW}}{V_{STW} + V_R}$

V_{STW} = volume of discharge from STW, m^3/day

V_R = river flow upstream of discharge, m^3/day

3.2 Use stage.

Where a chemical is used at a limited number of sites, then a similar approach to that for the manufacturing sites can be used, with the appropriate information on use patterns, wastage rates etc. For a chemical used in a domestic product, eg a detergent additive, the total amount of chemical can be considered to be discharged to the environment, via a treatment works. From population figures and the quantity of chemical, a figure of amount of chemical released per person per day can be calculated, and this can be used together with the number of people served by a STW to estimate the amount arriving at the treatment works per day.

3.3 Disposal stage.

This will not be considered in this exercise.

4 Information required.

For the chemical: production quantity
wastage rate as percentage of production
frequency of production
use pattern
wastage in use
physical-chemical properties (for absorption, and likely pathways to the environment)
potential for degradation and hydrolysis

Other information: chemical plant effluent volumes
river flows
sewage treatment works sizes

All of the above three could be specific to known production and/or usage sites, could be typical values for the country, or could be chosen to produce the "worst-case" situation.

In addition any information about similar chemicals and relevant industries would be useful.

B Effects

The amount of data on effects which is available at the first assessment level for new chemicals is small. Concentrating on the aquatic environment, there are four test results of use here: a fish LC50, Daphnia EC50, 5-day BOD, and octanol-water partition coefficient. The biodegradation test, which may be for longer than five days, will give some idea of the likely persistence of the chemical in the aquatic environment. An indication of whether the chemical is likely to accumulate can be obtained from the partition coefficient: a value of greater than 10^4 would give rise for concern here. If these two pieces of information do not suggest caution, then the lower of the values for fish LC50 or Daphnia EC50 is compared with the predicted environmental concentration obtained from the process above taking into account a safety factor. The safety factor used here, and for which there is some support, is 100. Thus, if the predicted environmental concentration is 1% or less of the lower of the two LC50 or EC50 values, then having taken into account the persistence and bioaccumulation potential data, the chemical should not give cause for concern at the tonnage considered.

The emphasis in this assessment method is on the aqueous environment, as this is the release route for many chemicals in the UK. The assessment should take into account other possible routes for the chemical, and the limited amount of mammalian toxicity data available if there is a possibility that mammals could come into contact with the chemical.

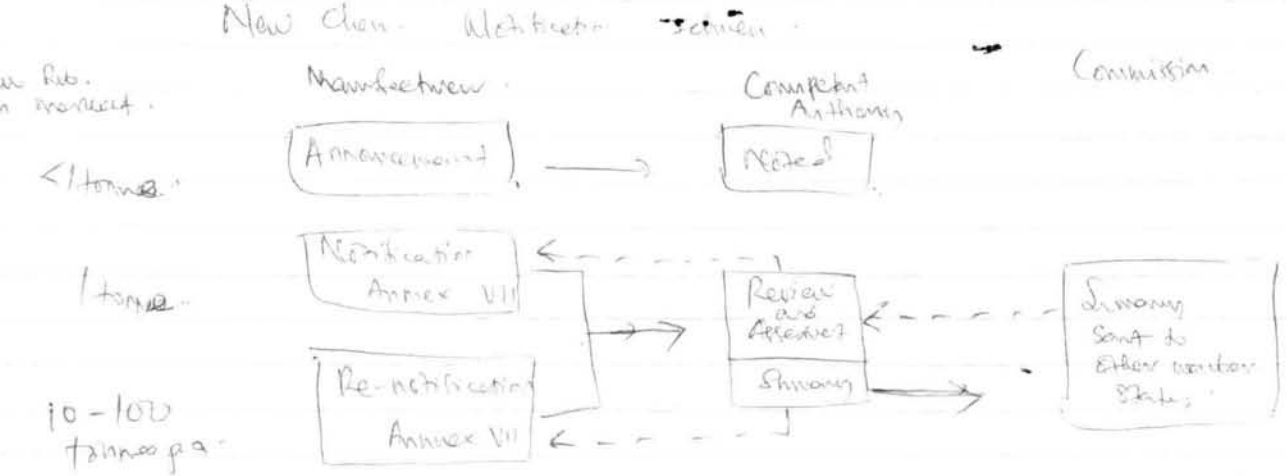
Further testing

The above procedure provides a basic screen to identify new chemicals which may cause problems (and could be applied to older chemicals too). If the predicted concentration exceeds the suggested toxic effect levels, then firstly an attempt would be made to review the calculations, perhaps by obtaining more detailed information on use and production from the manufacturer. If a problem is still indicated, then further relevant testing could be requested, again after discussions with the manufacturer. Also, bodies with regulatory powers such as the Water Authorities would be informed.

D. Brooke
PRL
Nov 1987

D. Brooke Dept. of. Environment. (Regulator provisions)

New chem. Notification scheme.



[Manufacturer]

Exp. of notifiable chem.:

Adhesives
Antioxidants
Capacitor fluids
Inks
Leather processing chem.

for full notification

Notifier name — manufacturer / importer
e.g. — identity
— quantity
— use
— method of detection and determination
— physical chem. properties
— reactivity / stability
— explosivity
Recommendations for — safe handling
— disposal
— destruction
— labelling.

Closed or knowledge (toxicity).
Notifier own assessment of the potential hazard.

Physico-chem. properties req. for Level 0.

- Melting point
- Boiling point
- Relative Density
- Vapour pressure
- Surface tension
- Water Solubility
- Fat Solubility
- Partition Coefficient
  - Flash Point
  - Flammability
- Explosive properties.

Toxicity test results required for Level 0.

Acute Toxicity
- oral
- Intraderm
- dermal
- Resp. Irritation
- eye irritation
- Skin sensitization

Sub acute - Toxicity
- oral
- Intraderm
- dermal

Mutagenicity
- one bacterial
- one mammalian.

Ecotoxicity test results req. for Level 0

Acute Toxicity
- fish
- Daphnia.

Degradation: Biotic
Degradation
- Aerobic: dissolved organic carbon, BOD.
- COD.

Degradation: abiotic - Hydrolysis as a function of pH.

Ecotoxicity test must required for level 1

Toxicity — algae
- higher plant
- earthworm

Prolonged Toxicity — fish
— Daphnia

Bioaccumulation — one species (preferably fish)

Biodegradation — prolonged, if not - proven at level 0.

Level 2-

Additional test should effect on food chain — accumulation
— degradation
— mobility

Prolonged toxicity — fish reproduction.

Acute and sub acute toxicity —

Inland ass of aquatic ecosystem — water to env'

— Direct to

500 mg/kg very toxic.

ENVIRONMENTAL ASSESSMENT OF CHEMICALS

NOTIFICATION OF NEW SUBSTANCE 'ROTSTOP 4'

Manufacturer: PRL Industries (Importer)

Identity of substance: organic acid

Quantity: 4 tonnes per annum; projected to rise to 400 tonnes per annum

Use: wood-treatment

Distribution: importer expects 20 customers for product

Physico-chemical properties:

Molecular weight:	266
Melting point:	101°C
Vapour pressure:	5×10^{-6} mmHg (6.7×10^{-7} kPa) at 19°C
Solubility:	14 m/l
Octanol-water partition coefficient:	1×10^{5} (neutral form)
pka	4.7

Mammalian toxicity: Acute:

Rat Oral LD 50: 135 mg/kg bw (F); 205 mg/kg bw (M)
Rat inhalation LD 50: 11.7 mg/kg bw

Skin irritation: irritant in pure form
Eye irritation: not tested, assumed
Skin sensitisation: no effect

Subacute:

2 month oral exposure to rat: no-effect level 2 mg/kg bw

Mutagenicity: Salmonella typhimurium, strains TA 98, TA 100, TA 1535 - no effect with or without S9 activation

Ecotoxicity: 96 h LC 50, rainbow trout: 0.08 mg/l
24 h EC 50, Daphnia magna: 0.8 mg/l

Biodegradation: no degradation in 5-day ready biodegradability test

Other information: importer estimates 1% wastage during use of chemical

$$\beta_w = \frac{Q}{NS} - \frac{w}{100}$$

ENVIRONMENTAL ASSESSMENT OF NEW CHEMICALS

NOTIFICATION OF NEW SUBSTANCE 'SOAKAWAY 10'

Manufacturer: Brooke Chemicals (Deturgents) plc

Identity of substance: long-chain organic acid salt

Quantity: up to 10 tonnes per annum

Use: ingredient in low temperature detergent powder

Distribution: manufacture will be at 1 site in the UK

Physico-chemical properties:

Molecular weight:	210
Melting point:	130°C
Vapour pressure:	3.1×10^{-6} mmHg
Solubility:	41 g/l
Octanol/water partition coefficient:	0.25

Mammalian toxicity:

Mouse LD 50 (oral): 25 g/kg body weight
Mouse LD 50 (dermal): >300 g/kg bw

Skin irritation: no effect
Eye irritation: mild irritation when pure substance applied
Skin sensitisation: no effect

Sub-acute toxicity: 28 day test on mice; no-effect level 400 mg/kg/day
(Gross pathology, liver examined)

Mutagenicity: Ames test, *Salmonella typhimurium*, Strains TA 100, TA 1535, TA 98
No effect with or without S9 activation

Ecotoxicity:

96 h LC 50, fathead minnow:	106 mg/l
24 h EC 50, *Daphnia magna*:	95 mg/l

Biodegradation: 5-day biological oxygen demand test: 10% degradation

Hydrolysis: no information

ENVIRONMENTAL ASSESSMENT OF NEW CHEMICALS

Background information

River flows in the UK

Median river flow: 2.4×10^4 m^3/day
25 Percentile: 6×10^3 m^3/day
75 Percentile: 1.5×10^5 m^3/day

Sewage treatment works

Typical works serves 10 000 people
Water usage average 240 l/day/person
Solids removed 80 g/day/person (dry weight)

Industrial direct discharge volumes

Typical chemical production plant: 450 m^3/day
Typical wood treatment plant: 5000 m^3/day

Possible further tests required for new chemical (ecotoxicity)

Algal toxicity
Higher plant toxicity
Earthworm toxicity
Prolonged fish toxicity
Prolonged daphnia toxicity
Bioaccumulation
Inherent degradability
Other degradation tests
Mobility test
Fish reproduction
Avian toxicity
Adsorption/desorption

S/12 Stages

FIVE STAGES

effect of chemicals

. IDENTIFICATION	- WHAT EFFECTS
. EVALUATION	- WHAT SIGNIFICANCE TO WHOM
. DEFINITION	- SOURCES, PATHWAYS, EXPOSURES - INTAKES AND UPTAKES
. MANAGEMENT	- WHAT CAN BE DONE AT WHAT COST & EFFECTIVELY
. DECISION-MAKING	- WHAT WILL BE DONE WITH WHAT RESULTS

Fig 1. Five Stages of a Risk Management

FIG. 2. DISTRIBUTION CURVE:
Blood lead concentrations
in the general population

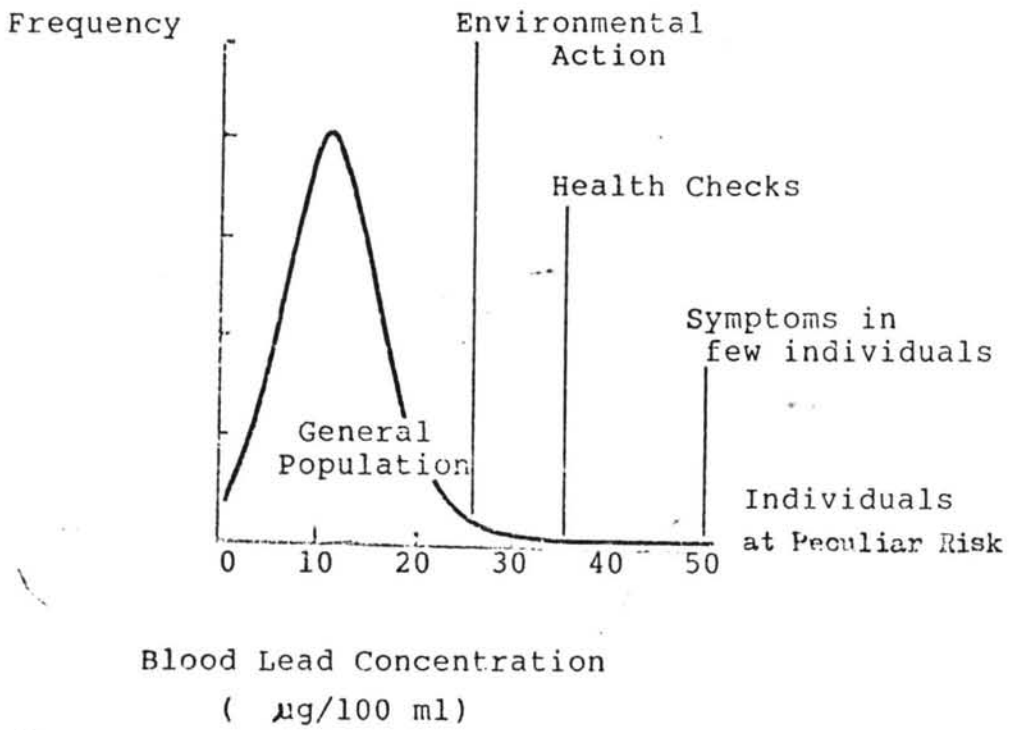


Fig 2. Distribution Curve: blood lead

Fig. 3. Accepted threshold values for blood level concentrations

THREE 'TRIGGER' VALUES

1. JUSTIFYING ENVIRONMENTAL INVESTIGATION : 25 µg/100 ml

2. JUSTIFYING HEALTH CHECKS OF THE INDIVIDUALS : 35 µg/100 ml

3. LIKELY TO GIVE RISK TO OBVIOUS SYMPTOMS IN A FEW PEOPLE : 50 µg/100 ml

Fig 3. Accepted threshold values for blood lead

ANTHONY ROWLAND AND PAUL COOPER
ENVIRONMENTAL HEALTH, (LONDON 1983) (Modified)

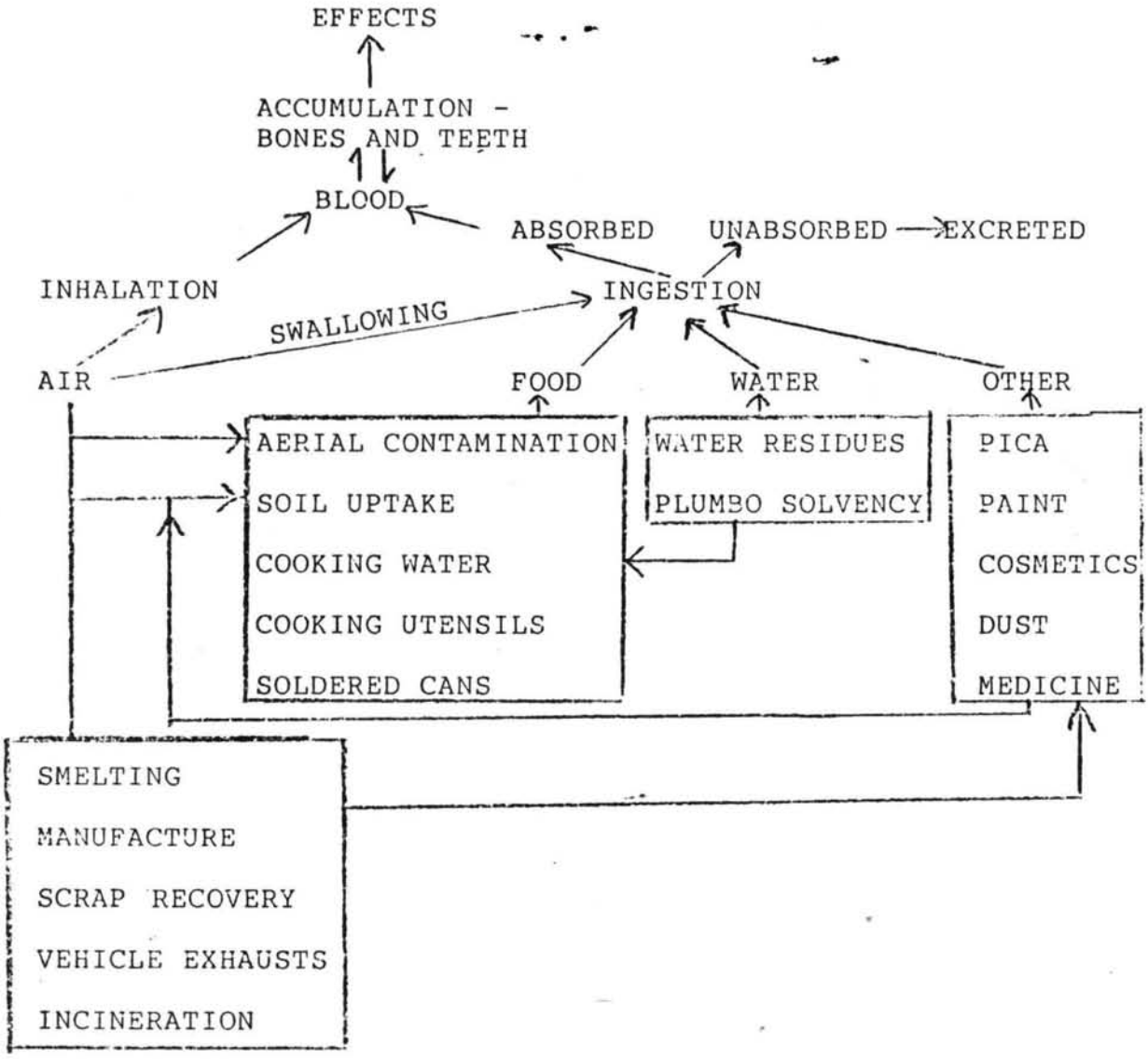


Fig 4. lead cycle.

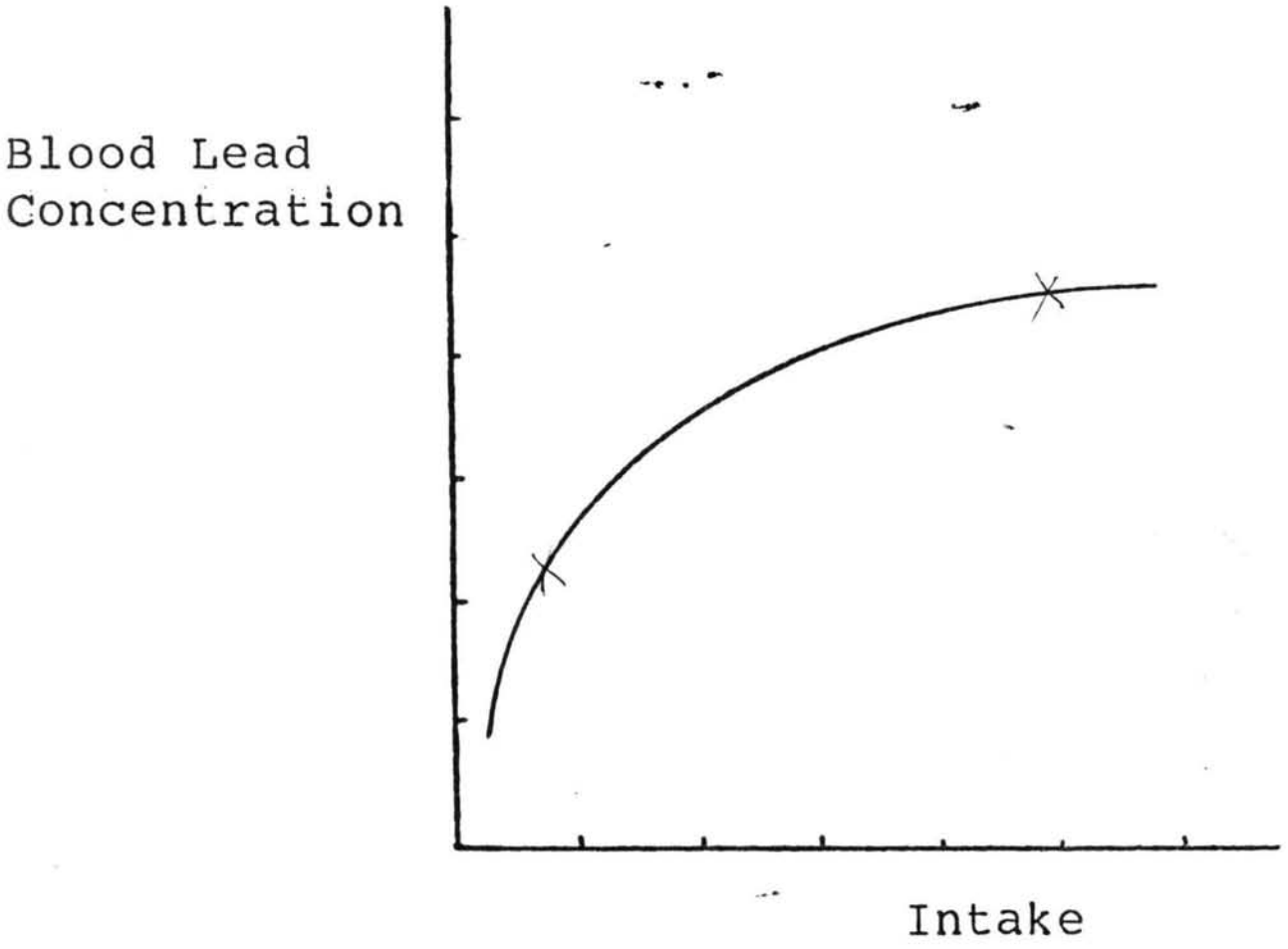
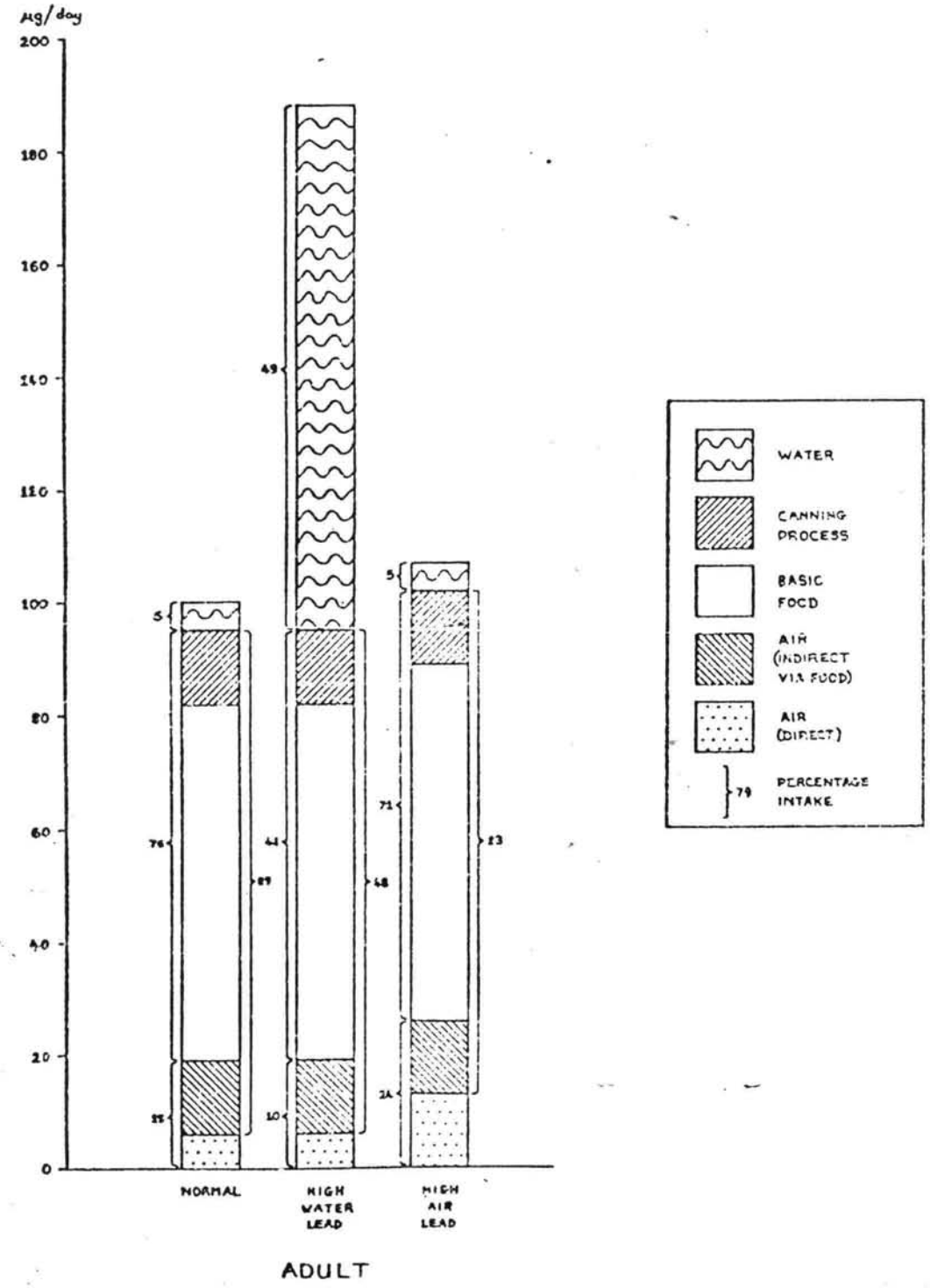


Fig 5a.
Relahonship between intake and blood lead concentrations

Fig. 5b. Estimated lead intakes for adult

FIG. 2

LEAD INTAKE



Normal urban environment and diet has: air - 0.43 ug/m^3; water 5 ug/l; diet - 90 ug/day (adult), 51 (child).

High water lead condition: 100 ug/l. High air lead condition: 0.86 ug/m

Fig 6b Estimated lead intakes for adult

Fig 6 Actions taken (both scales) FIG. 6. ACTIONS TAKEN

ANNEX

Source	Responsibility	Occurrence	Action in Hand
1. Lead from petrol	Supranational European Economic Community and national	General in cities but possibly greater for those near main roads	Action being taken in two stages: a. reduced to 0.15 g/l end December 1985 by UK Government b. reduction to 0 by 1989 within the European Community
2. Lead from cans	Supranational European Economic Community and national	General, but possibly slightly greater in social Classes IIIb, IV and V	Usage of lead to be phased out by manufacturers in the mid-1980s for UK and most European cans
3. Ordinary food	National	General	Regulations; limit imposed by Ministry of Agriculture, Fisheries and Food possible reductions from reduction in lead in petrol)
4. Smoking and drinking including passive smoking	Supranational and national	General (adults) (children – smoking mothers)	Limited to propaganda: modest increase in number of non-smokers; action with alcoholic drinks (and sales from older beer engines)
5. Water supplies with high lead concentrations	National and regional	Area specific and identified within limits	Remedial action being taken by Water Authorities: private water supplies taken by Local Authorities.
6. Old buildings - residential, industrial, education (paints, dusts)	National, regional, local	Local	Areas known; action - so far limited to measurements and advice

Source	Responsibility	Occurrence	Action in Hand
7. Discharges and emissions from metal-using industries	National and local	Very local	More stringent emission standards being imposed by Her Majesty's Industrial Air Pollution Inspectorate. Action by Local Authorities where appropriate.
8. Consumption of vegetables from contaminated gardens, allotments, unusual die or habits (surma)	Local	Local	Some areas known; possibility of identifying others; general advice given
9. Special category: burning lead cables, stripping lead paint, eating paint flakes	National, regional, local	Very local indeed	Advice
10. Homes of children of workers occupationally exposed to lead	National, regional, local	Local, associated with specific industries, factories	Advice; more stringent regulations in older scheduled industries; same regulations in newly scheduled industries
11. Glazes/plates	Supranational (EC) and national	General	EC Directive on release of lead in force

Dr D L Simms

8/0

Regulating Lead

Five Stage Analysis.

Insert Chart 1

Stage One

Identification: define damage by a scientific assesment of the evidence of its possible effects.

Lead is toxic, persistent and bioaccumulative. At high doses, even for short exposures serious effects on human health, intelligence and behaviour.

How certain is evidence that lead does harm at current concentrations due to environmental exposures? Comparative size of socio-economic factors; age of housing; class; hygiene ?

Can possibility that lead has some effect be ignored?

Stage Two.

Evaluation: examine the significance of these effects; estimate the size of the population at risk, identify the critical or most sensitive groups within it.

Can we take blood lead concentrations as a true indicator of body burdens and that threshold values may be set above which effects may occur.

Insert Chart 2.

What is the distribution of the geometric mean of the blood lead concentrations of adults and of children in the U.K? Do any factors cause wide variations?

Interpeting these Values.

Three 'trigger' values have been proposed in the United Kingdom.

Insert Chart 3

How would emphasis of the argument and conclusions change were these values too high or too low.

Estimating the Numbers at risk.

What is the percentage in the general population in the United Kingdom above 50 µg/100 ml, above 35 µg/100 ml, above 25 µg/100 ml?

Is there a separate group at risk? Does protecting them require a different set of policies?

Stage Three

Definition; (a) identify and quantify sources and pathways leading to exposure to lead, and (b) estimate intakes and uptakes, consider their relative importance.

Insert Chart 4.

How far is it ubiquitous, accumulative, persistent?; how many pathways to Man?

How do we quantify the size of each intake and its relative importance? Is the relationship between blood lead concentrations and exposure linear?

Insert Chart 5.

How far does total uptake depend upon habit? Does the uptake from drinking water vary with when it is drunk on its own than when taken with meals?

Intakes.

For Great Britain; variables include;

1). smoking and drinking of alcoholic beverages;

2). lead in drinking water;

3). air lead, mainly from petrol, by inhalation at current air lead concentrations, indirect routes, by transfer into dusts and thence to food;

How far do body burdens vary with local and personal circumstances?

Stage Four.

Management; set out scope for, the feasibility and costs of imposing controls, assess relative effectiveness, including speed of response, acceptability and enforceability.

1). identify areas in the Great Britain where the lead concentration in water is high;

2). lead added to petrol;

3). examine advances in technology,

4). changes in habits;

5). scope for more stringent controls on particular pathways.

Speed and Consequences.

What are the consequences and to whom? Do time-scales differ?

1), water supplies; what can be done? do pipes need replacing, can pH be controlled;

2), how long to produce lead-free petrol and engines to match?;

3), lead in paint;

4), changes to alcoholic beverages;

5), reduced cigarette consumption;

Stage Five,

Decision Making: relate the results of the previous four stages to pubic sensitivity to the effects and their consequences, Include social values as well as costs,

Comparative attitudes,

Does lead appear in the tables giving indicators of health? What are consequences of effects? Why do they arouses considerable emotion?

How far are the exposures avoidable? How effective?

The need for Action,

Assesment of the importance and the size effects?

The feasibility and enforcement of Controls,

Crucial questions; what controls are necessary, feasible, acceptable and enforceable and how swift relative to their cost and to each other - and who pays;

External pressures; Government and Industrial

Insert Chart 6

1), past industrial emissions and their depositions?

2), do technology and the market combine?

3), how does expense of replacing lead pipes compare withnormal rates of expenditure?

4), how radical are the changes for engines run on lead-free petrol,

Monitoring the results

How can a monitoring programme be devised? What should it try to do?

8/12

Regulating Lead

Five Stage Analysis,

Insert Chart 1

Stage One

Identification; define damage from lead by a scientific assesment of the evidence of its possible effects,

Lead is toxic, persistent and bioaccumulative, At high doses, even for short exposures serious effects on human health, intelligence and behaviour,

No certain evidence that lead does harm at current concentrations due to environmental exposures in the U,K, Socio-economic factors; age of housing; class; hygiene have effects at least of similar size,

On balance, the possibility that lead has some effect cannot be ignored,

Stage Two,

Evaluation; examine the significance of these effects; estimates the size of the population at risk, identify the critical or most sensitive groups within it,

Assume blood lead concentrations are a true indicator of body burdens and that threshold values may be set above which effects may occur,

Insert Chart 2,

The geometric mean of the blood lead concentrations of adults and children in the U,K, is 11 µg/100 ml, Values and

the distribution curves are the same everywhere except for inner city areas and those places where the lead concentrations in drinking water are higher than average.

Interpeting these Values.

Three 'trigger' values have been proposed in the United Kingdom.

Insert Chart 3

Agreed that children are most at risk.

The emphasis of the argument and some of the conclusions will change if subsequent research shows these 'trigger' values to be too high or too low.

Estimating the Numbers at risk.

The percentage in the general population in the United Kingdom above 50 µg/100 ml, the highest of these trigger values, is effectively zero; very few are above 35 µg/100 ml and a small number above 25 µg/100 ml.

Separate group at risk. Few children with very high blood lead concentrations in the U.K. are almost always found to have access to some particular high exposure, such as lead in paint or to suffer from pica. Protecting them requires a second set of policies.

Stage Three

Definition: (a) identify and quantify sources and pathways leading to exposure to lead, and (b) estimate intakes and uptakes, consider their relative importance.

Insert Chart 4.

Ubiquitous, accumulative, persistent; many pathways to Man; inhalation and ingestion via the air and the ingestion from food, water and wine. Lead in food, comes from many different sources.

Considerable difficulties in quantifying the size of each intake and its relative importance. The relationship between blood lead concentrations and exposure is not linear.

Insert Chart 5.

Total uptake depends on habit; uptake from drinking water higher when the water is drunk on its own than when taken with meals.

Intakes.

For Great Britain;

1). average smoker and drinker of alcoholic beverages has a blood lead concentration of about 20% more than those who neither drink nor smoke;

2). effects of lead in drinking water are substantial;

3). comparatively small difference between suburban, rural, and even inner city areas suggests that air lead, mainly from petrol, by inhalation at current air lead concentrations, is not important. Indirect routes, by transfer into dusts and thence to food, suggested as important, little evidence that this is so.

Body burden varies with local and personal circumstances. Prudent to seek to reduce exposure from all sources as far as it is practicable to do so.

Stage Four.

Management: set out scope for, the feasibility and costs of imposing controls, assess relative effectiveness, including speed of response, acceptability and enforceability.

1). identify areas in the Great Britain where the lead concentration in water is high;

2). lead added to petrol;

3). advances in technology produced the two-piece can ,

4). and the need to add lead to paint;

5). much less coal is burnt in domestic grates today reducing the amount of lead released;

6). more stringent controls on particular pathways, reduce the amount of lead permitted in food for sale.

Speed and Consequences.

Different consequences to blood concentration over different time scales;

1). water supplies; relatively long in some areas, where pipes need replacing, but short where pH can be controlled; reductions in the average blood lead concentrations are likely to be substantial and very large for some individuals;

2), lead-free petrol and engines to match is long; gradual drop in the blood lead concentrations, with a subsequent more gradual drop as food and dusts cease to be contaminated;

3), action on lead in paint may only effect children in inner cities, may take a very long time indeed;

4), changes to alcoholic beverages; immediate effect those who drink;

5), reduced cigarette consumption; immmediate and on children of mothers who smoke.

Stage Five,

Decision Making; relate the results of the previous four stages to pubic sensitivity to the effects and their consequences, Include social values as well as costs,

Consider the effects of other countries' actions, especially the European Economic Community. What are prospects for exports of cars, etc., if some change and others do not? Comparative attitudes.

Lead does not normally appear in the tables giving indicators of health. Lead rouses considerable emotion because; its effects fall into the same category of 'Fates worse than death',

These have serious socio-economic consequences, to the individuals, to their families and to the societies in which they live. Our society does not meet them.

Reinforcing those emotions, the bulk of the exposures are imposed by others. The individual can avoid alcoholic

beverages, stop smoking live in a newer house, and practice high personal and social hygiene. Important, but is unlikely to be large for those most at risk.

The need for Action.

Insert Chart 6

The need for action must in the first place depend upon the assesment of the importance and the size effects. Were the opinion that the effects were huge, action almost regardless of cost would be essential.

The feasibility and enforcement of Controls.

Crucial questions; what controls are necessary, feasible, acceptable and enforceable and how swift is each of them relative to their cost and to each other - and who pays;

1). for past industrial emissions and their consequent depositions little can be done; clean-up is expensive;

2). comparatively straightforward and quick if the technology and the market combine; new, safer glazes in ceramics, the two-piece lead free can, the plastic external cover for car batteries;

3). replacing lead pipes for drinking water expensive compared with normal rates of expenditure;

4). radical changes; e.g., modifying engines to be capable of running on lead-free petrol.

Monitoring the results

Ubiquitousness, the large number of sources and pathways, makes it difficult to devise a monitoring programme. Needs to show changes in body burdens and which changes are responsible for how much and how quickly.

9/12 87 London.

G Chester Pesticides & Products

Pesticide groups

	% used worldwide
Herbicides	44
Insecticides	31
Fungicides	17
Rodenticide	8
Miscellaneous (PGR, Biocides)	

Pesticide product safety relies on

- manufacture
- formulation
- packing
- storage
- transport
- use
- disposal

Acute toxicity testing data

Test	Relevance	
Acute oral LD_{50}	swallowing	- accidental - deliberate
acute dermal LD_{50}	handling	- diluted product - dermal contact
acute inhalation LC_{50}	handling	volatile / dusty powders
Irritancy - skin - eye	handling	- care. paint - skin / eye cont.
Sensitisation	all applied product.	

Mutagenicity testing

Philosophy in testing in vitro (culture) to ascertain whether a compound has mutagenic potential.

NO : — no work

Yes — Studies in vivo.

mutagenicity testing

- point mutation
- chromosome
- DNA

margin of safety

Factor of diff. between no observable eff. level (mg/kg bodyweight/day) & predicted

operator monitoring

exposure determination
absorption measurements
biological monitoring

exposure: dermal >> inhalation
of pesticides

absorbed dose = % dermal dose absorbed × exposure

(% absorption method)

(laboratory study) ↓ field study

measurement of dermal penetration

in vivo — animal model
— human volunteers

in vitro - diffusion cell

PESTICIDE CASE STUDY

1. INTRODUCTION

The test case compound is a non-selective translocated herbicide which is used against a wide spectrum of grasses and broad-leafed weeds when applied as a foliar spray. It is used : around established apple and pear trees between harvest and the followimg summer; pre-planting weed control before planting kale, maize, oilseed rape, potatoes and wheat; on fallow land and in other non-crop situations. The use pattern is such that workers are exposed only intermittently to this product.

2. PHYSICO-CHEMICAL DATA

A white crystalline solid
Molecular weight : 84
Melting point : 150-153°C
Solubility : soluble in water to extent of 28 g/100 g and in ethanol and methanol to extent of 26 g/100 g. Sparingly soluble in ethyl acetate and insoluble in ether, acetone and most other organic solvents.
Stability : breaks down in UV light

3. BIOTRANSFORMATION

The compound is rapidly excreted from the body. Following intraperitoneal administration, at least 90% of the injected dose was observed in the urine unchanged within 24 hours.

When fed to rats, 70-96% of the radioactivity was excreted during the first 24 hours as the parent compound and 2 unidentified metabolites. After absorption, the compound was distributed throughout most of the body tissues. Elimination from all tissues was rapid. The liver contained a metabolite but no free parent compound. The rate of elimination of the metabolite was much slower than that of the parent.

4. EFFECTS ON ENZYMES AND OTHER BIOCHEMICAL PARAMETERS

Acute administration of the compound results in depression of catalase and peroxidase enzyme activity as well as the activity of several other enzymes. Liver peroxidase recovered within 24 hours, while liver and kidney catalase depression was slower to recover. Catalase returned to normal after 7 days.

Groups of 15 male rats were administered radioactive iodine alone or in combination with 0.15 or 0.78 mg/kg compound by intraperitoneal injection. Uptake of radioactivity was significantly depressed at 0.78 mg/kg. The lower dose reduced iodine uptake but the reduction was not statistically significant.

The compound exerts effects on various other biochemical systems and enzymes associated with oxidative metabolism.

5. CARCINOGENICITY

MOUSE

The compound was administered orally to groups of mice from day 7 to day 28 of age at doses of 1000 mg/kg and thereafter in the diet at a dose of 2192 ppm (maximum tolerated dose). None of the mice survived the 18 month test period.

Hepatomas were evident in most animals (67/72), and carcinoma of the thyroid was reported in 67/71 of the animals examined.

In a further study the compound was administered at 1% (greater than maximum tolerated dose) in the diet and produced a carcinogenic effect; however, it was found to be an antitumour agent when combined with certain other carcinogenic stimuli. The carcinogenic effect was prominent in the livers of C3H mice; thyroid tumours were less common because they required a longer period of development and the lifespan of the mice was shortened by the compound in the diet. The inbred C3H actalasemic mouse substrain developed more liver tumours, starting earlier, than did the C3H normal catalase substrain. These findings indicated a possible relevance of catalase and H_2O_2 in carcinogenesis.

RAT

In rats administered 10, 50 or 100 ppm of the compound in the diet for 104 weeks, thyroid adenomas developed in 1/10, 2/15 (1 "adenocarcinomatous") and 17/26 (4 "adenocarcinomatous") rats treated at the three dose levels. No tumours were found in 5 controls examined.

In rats administered diets containing 0, 10, 50 or 100 ppm of the compound for 104 weeks, those receiving the 100 ppm level showed a high incidence of thyroid adenomas (15/27 rats examined). The incidence was lower (1-3/27 rats) in the groups given 10-50 ppm.

A high incidence of thyroid and liver tumours was observed in rats following oral administration of the compound in drinking water (20-25 mg/kg/rat) or in the food at 2 dose levels (250 or 500 mg/rat/day) for lifespan, which varied from 10-32 months. At the time the first thyroid tumour was found a total of 28/55 (drinking water) and 26/49 (diet) thyroid tumours were evident. At the time the first liver tumour was detected, a total of 15/44 and 17/52 developed benign and malignant liver tumours, respectively. Concurrent daily injections of 2.5 µg/100 g b.w. thyroxine and oral administration of 300 mg/day/rat of the compound in food for the duration of the study resulted in the development of only one thyroid adenoma but of 9 liver tumours in 12 males. The compound alone induced thyroid tumours in 7/22 and liver tumours in 12/23 male rats of the same age. No liver tumours but 2 thyroid cystic adenomas were observed in 50 control animals.

Forty female Wistar rats were given 2500 ppm of the compound in the drinking water during their lifetime. Of these, 26 survived for more than 30 weeks and goitre was observed in all. The proliferating follicular tissue of the thyroid gland gave invasive lesions in 19 of the 26 surviving rats. In a second group of 30 rats with partial thyroidectomy and also given 2500 ppm of the compound in the drinking water, the invasive lesions were more frequent in the 15 surviving rats.

In a further study, female Wistar rats were given 2500 ppm of the compound in the drinking water for 60 weeks in combination with ethylenethiourea or with a low iodine diet. Goitres, which were defined as enlargement of the thyroid due to hyperplasia of the follicular tissue, developed in all rats given the compound, ethylenethiourea or a low iodine diet and follicular carcinoma with invasive growth were also found in significantly high incidences in these groups. No synergistic effects in the development of follicular carcinoma were seen in rats given combinations of the compound and ethylenethiourea, or a low iodine diet.

In a 2 year feeding study, groups of rats were fed 0, 10, 50, 100 and 500 ppm of the compound in the diet. Various thyroid abnormalities were observed, including enlargement (100 and 500 ppm), hypofunction (10 ppm and above), hyperplasia (50 ppm and above) and adenomas (100 ppm). (The 500 ppm group were taken off at 13 weeks). No hepatomas were reported. A no effect level was not observed and 10 ppm was a minimum effect level.

DOG

Dogs (2-4/group) were administered diets containing 0, 10, 50, 100 or 500 ppm of compound for 52 weeks. No tumours were detected in the thyroids or in other organs.

6. SHORT-TERM STUDIES

RAT

The compound was administered to rats at 1000 mg/kg by intraperitoneal injection on alternate days for 42 days. There was no effect on b.w. gain or food consumption; however there was a 3-4 fold increase in thyroid weight.

Daily administration of the compound to rats, 5 days per week for four weeks at 0, 100, 200 and 400 mg/kg resulted in reduction in growth rate, increase in relative thyroid weight and decreased iodine content of the thyroid.

Administration of a high dose of the compound in drinking water (60 mg/kg/day) produced goitres in rats in 3 days. Rats were fed dietary concentrations for 32 days. One group received 500 ppm for 32 consecutive days, another group received 1000 ppm on alternate days for the duration of the study and a group was fed the basal diet. Behaviour and mortality were not affected. Food intake and growth at 500 ppm were reduced. Food intake and growth at 1000 ppm on alternate days did not differ significantly from the controls. At autopsy, the thyroid gland

was hyperaemic and enlarged at 500 ppm whereas that of animals fed 1000 ppm was only slightly hyperaemic but otherwise comparable to the controls. Mean thyroid weight/bodyweight ratios for the 0, 1000 and 500 ppm groups were 58, 77 and 303 respectively.

Groups of rats were fed dietary levels of the compound for 11-13 weeks at 0, 0.25, 0.5, 2, 10 and 50 ppm. At 0.5 ppm no effect was observed in any of 7 separate measurements of thyroid function although iodine uptake was slightly reduced and serum "Protein Bound Iodine" (PBI) concentrations were slightly increased. Significant effects were noted at 2 ppm in the diet, especially with regard to reduced PBI and reduced iodine uptake by thyroid.

DOG

Groups of dogs were fed 0.25, 1.25, 2.5 and 12.5 mg/kg of the compound orally by gelatine capsule 6 days/week for 52 weeks. There was no mortality. Growth, appearance and behaviour were normal in all test animals. Results of biochemical, haematological and urological examinations were normal. Gross and microscopic examination of tissues and organs showed no evidence of abnormality associated with the test compound.

7. REPRODUCTIVE STUDIES

RAT

Groups of rats were fed the compound in the diet at levels of 0, 25, 100, 500 and 1000 ppm for 2 months and mated. Numbers of pups and survival were reduced at 500 and 1000 ppm. These doses were terminated. The remaining doses were fed through 2 generations. At 1000 ppm there was no effect on reproduction or survival. However, all animals had thyroid hyperplasia. The incidence of hyperplasia at 25 ppm was sporadic.

Oral administration of the compound at 400 and 1000 mg/kg resulted in no signs of foetotoxicity or of teratogenic effects. Moreover, oral administration of 100 mg/kg or 100 ppm in the drinking water for 3 months before mating and in females up to day 15 of gestation was without effect on reproduction in either males or females.

8. MUTAGENICITY

The compound has been shown to be negative in the following assays :

Ames, Escherichia, Drosophila, Human Lymphocytes, Aspergillus Nidulaus, Mouse Lymphoma, Micronucleus, Effects on DNA, S Cerevisiae, Sperm Effects.

The compound was positive in the following assays :

Cell Transformation, Chinese Hamster Ovary Cells (sister chromatid exchanges).

9. HUMAN DATA - CARCINOGENICITY

The compound has been produced industrially since 1955 with no evidence of ill effects other than mild contact dermatitis to the occupationally exposed workers. Sixteen employees were exposed for 5 to 6 months per year and 9 employees were exposed for approximately 10 months per year with no ill effects. No thyroid or liver tumours were observed "in excess of the general population".

A cohort study of 348 railroad workers has been reported in which the minimum exposure to 3 compounds, including the test compound was 45 days. There was a deficit of deaths from all causes (45 observed, 49 expected), but an excess from malignant neoplasms (17 observed and 12 expected). In workers exposed to the test compound only, there were 5 deaths from cancer (2 lung, 1 pancreatic, 1 reticulum cell, 1 sinus) with 3 expected. In those workers exposed to all 3 compounds there were 6 deaths from cancer with 3 expected. The men of the cohort were exposed to other organic and inorganic chemicals as well as the 3 compounds in question.

Fifty-seven pesticide operators, some of whom had used the test compound were studied for the incidence of sister chromatid exchanges in peripheral blood lymphocyte chromosomes. Overall there was no difference between the control group and the sprayers.

10. TOXICOLOGICAL EVALUATION

Levels causing no toxicological effect

Rat : 0.5 ppm in the diet, equivalent to 0.025 mg/kg b.w.
Dog : 12.5 mg/kg b.w.

PESTICIDE CASE STUDY

Identity of Compound :

Amitrole (3-amino-S-triazole)

EVALUATION

Amitrole was the subject of FAO/WHO evaluation in 1974 and 1977. The Joint Meeting on Pesticide Residues concluded that amitrole is goitrogenic on continuous long-term exposure, probably as a result of continuous inhibitions of peroxidase activity. In two long-term studies, hepatomas were produced in mice and rats administered amitrole at exceptionally high levels. However, a long-term feeding study at high dietary levels in rats did not result in hepatomas. In a one year dog study, no hepatic, goitrogenic or other effects were noted at a dietary level of 12.5 mg/kg b.w. The NEL was based on a short-term study where normal PBI values were noted at 0.5 ppm. In addition, since no goitrogenic effect on discontinuous exposure was noted, a conditional ADI was allocated.

JMPR was reassured that in the use of amitrole, man has only a remote, if any, chance of achieving the conditions where continuous exposure is maintained. It was emphasized that the ADI was allocated with the condition that the uses of amitrole be restricted to those where food residues would be unlikely to occur. Further, it was recommended that the use of materials in combination in the same formulation be restricted, especially where effects on specific target organs are expressed by both materials.

Estimate of Conditional ADI for man :

0.00003 mg/kg b.w.

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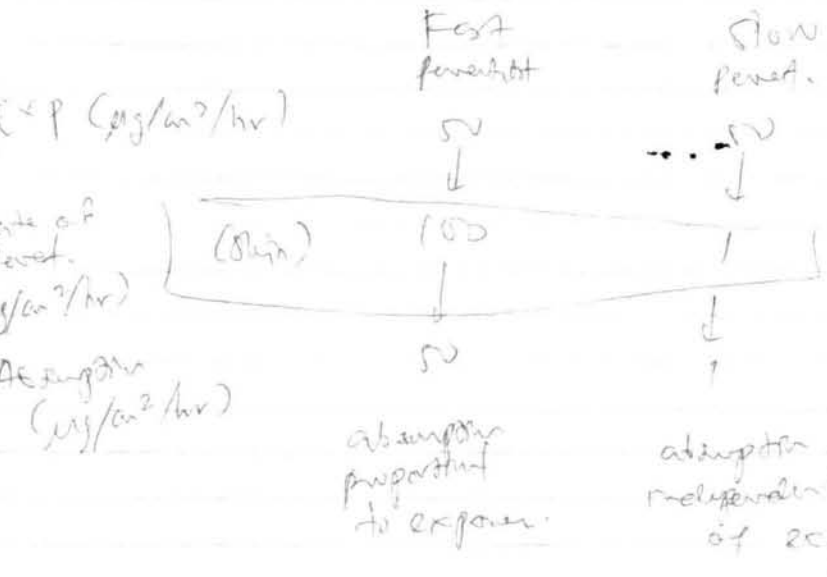
relationship between exposure rate of penetrating amount of absorbed



~~one cell of each organ is treated with each penetrant.~~

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C - CONSUMERS. J Barlow's

Dr S Barlow

what level of EC is acceptable

DHSS/IPCS RISK ASSESSMENT SEMINAR 9 DECEMBER 1987

ETHYL CARBAMATE IN ALCOHOLIC BEVERAGES

1. Introduction

Ethyl carbamate (EC), also known as Urethane, has been found in alcoholic drinks and in fermented foods such as bread, yoghurt and soy sauce. It also has a history of use as a hypnotic, anti-cancer agent and for symptomatic relief of asthma in human medicine, but has long since been replaced with more effective drugs in most pharmacopoeias. It has been (and is still used as an anaesthetic for experimental animals. The matter first came to public attention in November 1985 when extremely high levels (up to 20,000 ppb) of EC were reported by the Canadian authorities in some Canadian produced ports and sherries and also in some imported fruit spirits. Further work in Canada and subsequently in many other countries has shown its occurrence in alcoholic drinks to be widespread, but generally at levels much lower than 20,000 ppb. Detailed information on levels of EC found in UK analyses of alcoholic drinks is given in section 4 below.

The origins of the EC found in alcoholic drinks are currently the subject of considerable speculation and research effort. It is found in some wines and so must be a product of the wine producing process, most probably the fermentation. However, it is not found in beer to a great extent, so different types of fermentation process presumably yield different amounts. Levels in distilled spirits are much higher than in non-distilled spirits, (higher than can be accounted for by the simple concentration factor of distillation. It is also known that EC present before distillation (ie from fermentation) is destroyed then reformed during the distillation process and the reasons for this are not known. In addition there is evidence that after manufacture of fruit spirit drinks is completed further EC may be formed during storage of these beverages in the presence of light. An early theory that the use of urea as a permitted yeast nutrient in North America contributed to EC formation has now been discounted.

2. Physico-chemical properties

Synonyms: urethane, urethan, ethyl urethan, carbamic acid ethyl ester, ethyl carbamate.

Chemical Formula	:	$H_2N-\overset{\overset{O}{\|}}{C}-OC_2H_5$
Molecular weight	:	89.09
Melting point	:	48-50°C
Boiling point	:	182-184°C
Solubility	:	1g in 0.5 ml water))At 25°C 1g in 0.8 ml alcohol)

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Boiling point	:	182-184°C
Solubility	:	1g in 0.5 ml water))At 25°C 1g in 0.8 ml alcohol)

Stability	:	1.0 mM in 12% (v/v) aqueous ethanol, at pH 1.5 and 37°C, no significant reduction over 80 min
Volatility	:	Sublimes readily at 103°C at 54 mm Hg, volatile at room temperature

3. Biological activities

(a) Absorption, metabolism and excretion

In animals EC in aqueous solution is well absorbed and evenly distributed in the tissues and it crosses the placenta freely (1, 2). When radiolabelled EC was given to one mouse in aqueous solution high levels of radioactivity were seen in salivary, seromucous and Harderian glands, medullary bone, liver, bile and epithelia of stomach and intestine. Lower levels were seen in brown fat, thymus and oesophagus. Another mouse was given radiolabelled EC in 12% ethanol solution and whilst some radioactivity was seen in Harderian, seromucous and salivary glands most of the radioactivity remained confined to the lumen of the stomach and intestine, suggesting that the presence of ethanol inhibits absorption of EC (3). Elimination of EC injected i.p. into mice varies with age; 20% is eliminated in 24h in newborns and 75% in 6h in adults. This has been attributed to the immature mouse's lack of a liver esterase which converts EC to carbon dioxide (4). In mice 90% of an administered dose is excreted as CO_2 in exhaled air within 24h and the remainder is equally divided between urinary excretion and a retained portion (5, 6). In rats, rabbits and humans 0.5-1.7% of a dose is excreted unchanged in the urine (7). EC is ultimately metabolised to ammonia, carbon dioxide and alcohol, via N-hydroxylated intermediates and it is these intermediates which are carcinogenic, not EC itself. Small amounts of N-hydroxy urethane, acetyl-N-hydroxy urethane, ethyl mercapturic acid and N-acetyl-5-ethoxy carbonylcysteine are found as urinary metabolites. N-oxidation of EC to form N-hydroxy urethane, N-hydroxy esters or free radicals leads to biologically active ethoxycarbonylating or ethylating species which can bind to DNA (7).

(b) Toxicity in man

Therapeutic doses have been in the range 1-2g. Side-effects have not occurred at dose rates of 0.5g/day. Dosages of 1-2g given for short periods to relieve asthma were not accompanied by side-effects or narcosis. Doses of 3g/day for 20 days were associated with anorexia, nausea, vomiting, loss of weight and severe depression of the bone marrow (8). There are no human data on the carcinogenicity of EC.

(c) Mutagenicity

EC has been extensively tested for mutagenic activity (9). *In vitro* studies in bacteria, fungi and mammalian cells have given inconsistent but mostly negative results, probably due to the failure of the cells used and/or the added metabolic activation systems to adequately metabolise EC to an active form. EC has been shown to be clearly positive in a number of tests for cell transformation unless metabolic activation was lacking in which case it was negative. It is weakly mutagenic in Drosophila assays (sex-linked recessive lethal mutations and loss of sex chromosomes). *In vivo* it is clearly mutagenic, producing point mutations, chromosomal aberrations and sister chromatid exchanges in somatic cells in a number of species. EC, or more likely metabolites of EC, bind covalently to DNA and RNA in a number of tissues (liver, lungs, stomach, skin). It is known to reach germ cells, but has given negative results in several different types of germ cell mutation assays (rodent dominant lethal, mouse heritable translocation, mouse specific locus).

(d) Carcinogenicity in animals

EC has long been known to induce tumours in experimental mice, rats and hamsters, when given orally in drinking water or by stomach tube, by skin application, i.p., s.c. or i.m. injection, inhalation or intratracheal dosing. Lung adenomas, thymic lymphomas, forestomach papillomas, liver adenomas, haemangiomas and haemangiosarcomas, mammary adenomas and carcinomas, Harderian gland adenomas and various types of skin tumours have all been observed. It is carcinogenic in single dose experiments and following prenatal exposure. Neonatal and infant rodents are more susceptible to cancer induction by EC than adults. (See ref 10 for review of all these studies).

The studies detailed below have been selected from the many that have been carried out on EC because they offer dose-response data that may be used for risk assessment.

Schmahl et al (1977) reported dose studies in the Sprague Dawley rat and the NMRI mouse, fed urethane in their drinking water(11). The animals were kept until they died or became moribund. The results are summarised in Table V.

Table V.

URETHANE, CHRONIC FEEDING TO SD RATS AND NMRI MICE.
SURVIVAL PATTERNS AND FINAL YIELDS OF TUMOR-BEARING ANIMALS

	Daily dose (μg/kg)	n	n_{eff}	Surviving animals at days after beginning of the experiment (% of effective animal number)						n_m	%[1]	n_b	%[1]
				300	400	500	600	700	800				
Rats:	0	77[2]	74[3]	97	54	14	5.4	0		2[4]	2.7	1[5]	1.4
	100	74	70	100	61	37	29	16	0	2	2.8	3	4.3
	500	69	65	100	66	29	18	0		4	6.2	2	3.1
	2,500	73	70	98	63	39	23	0		7	10	5	7.1
	12,500	76	74	96	68	32	18	0		15	20	8	11
Mice:	0	78	74	92	86	69	50	27	0	6[6]	8.1	2[6]	2.7
	100	70	65	97	92	66	37	17	0	11	17	11	17
	500	72	69	94	86	67	30	8.7	0	17	25	12	17
	2,500	70	59	95	92	66	41	27	0	21	36	21	36
	12,500	69	65	94	82	54	23	0		32	49	30	46

[1] Percentage of effective animal number. — [2] n = total number of animals, minus animals not examined because of autolysis or cannibalism. — [3] n_{eff} = effective animal number: animals examined which were alive when the first animal died with tumor (in rats after 273 days, at 12,500 μg/kg/day; in mice after 181 days, at 2,500 μg/kg/day). — [4] n_m = animals dead with malignant tumor or leukemia. — [5] n_b = animals dead with benign tumor. — [6] Animals dead later than after 730 days excluded.

Risk estimation depends upon this study.

4. Exposure

ESTIMATES OF DIETARY INTAKE OF ETHYL CARBAMATE

	Number of Samples	Range ppb	Value Chosen ppb	Average Consumption l/year	Intake µg/year	Approx Extreme Consumption mg/yr
Whisky	17	8-230	50	2.75	137	2.3
Vodka	3	< 5	0			
Gin	3	< 5	0			
Liqueurs	13	< 5-438	50	.5	25	2.3
Wine	35	< 5- 17	8	12.2	97	1.5
Port	4	13-20	15	.1	1.5	1.8
Sherry	20	5-211	40	.9	36	5
Brandy	3	< 50	50	.6	30	2.3
Beer	10	< 1-1.6	0.5	150	75	0.2
Fruit spirits	1	1600	2000[a)]	0.05	100	90
Bread	10	< 4	0			
Yoghurt	10	< 1	0			
				Total	501.5 µg/yr	

a) Although only one sample was analyzed by the Food Science Laboratory, other laboratories have consistently found fruit spirits containing up to 10,000 ppb.

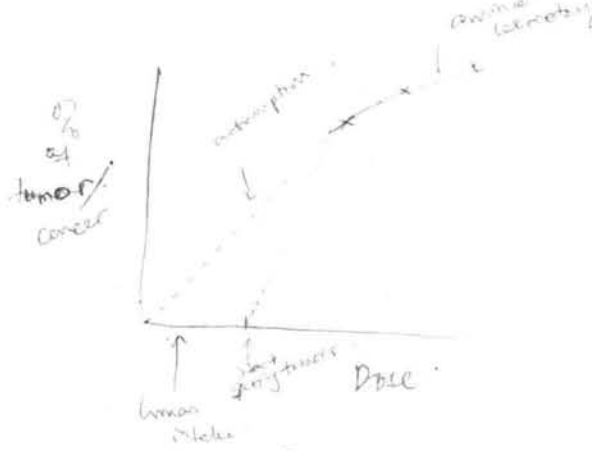
5. Risk Assessment

The risks of cancer for the rat and mouse have been estimated by three groups of experts. The models did not take species variation into account. The results are highly diverse; they are set out below.

Schmahl et al (11)

Two slopes were used in the calculation of the Mantel-Bryan procedure: the usual slope=1, and an observed slope=0.4. The "virtually safe dose" calculated was for a risk of $1/10^5$, for rats.

Mantel-Bryan (slope=1)	2,200 ng/kg b w
Mantel-Bryan (slope=0.4)	0.024 ng/kg b w
Liniar extrapolation	420 ng/kg b w



Schlatter (12)

The virtually safe dose calculated was for a risk of $1/10^6$

Model	Rat (ng/kg b w)	Mouse (ng/kg b w)
One-hit	60	20
K-Stage	60	20
Multi-hit	0.005	10^{-12}
WEIBULL	0.01	5×10^{-10}

Health and Welfare, Canada (13)

This is quoted verbatim..

"Three seperate approaches were considered for purposes of risk assessment. The first two methods required a study wherein a dose-effect relationship was observed. The only study which compiled withthis requirement was that of Schmahl et al (1977).

METHOD 1

The no observed effect levels (NOEL) for mice and rats were 500 and 2500 μ g/kg body weight, respectively. Based on a consideration of parameters relating to tumour profiles in rats versus mice and the incidence of tumours as reported in the Schmahl studies together with factors such as the treatment time (i.e. related to the occurrence of an unspecified virus infection), etc., a NOEL for rodents was estimated to be of the order of 1500 μ g/kg body weight. In view of other available data on the carcinogenicity of this substance, the deficiencies associated with this study and the absence of any other studies where multiple doses of ethyl carbamate were given, a safety factor 5000 was applied to this NOEL to estimate a tolerable daily intake (TDI) for humans of 0.3 μ g/kg body weight.

METHOD 2

The data from both the mouse and rat studies conducted by Schmahl were analyzed statistically and virtually safe doses (VSDs) were calculated based on both the probit model and using linear extrapolation. However, in view of the extremely variable results obtained (i.e. more than an order of magnitude different), there was a general lack of confidence in this approach and, as a result, method 2 was not considered further in the calculation of the tolerable daily intake.

METHOD 3

Method 3 involved the calculation of a VSD on the basis of TD_{50} values (i.e. the daily dose required to produce tumours in 50% of the exposed animals over a standard lifetime and adjusted for background incidence) (Gold et al., Environmental Health Persepctives, 58, 9-319, 1984).

The findings from all seven studies were considered as part of this approach. TD_{50}-values were calculated for each species and for each tumour with statistically significant difference. The average TD_{50} for 45 different tumours in 4 species (mouse, rat, hamster and monkey) was 130 mg/kg body weight. The average TD_1 was 2.6 mg/kg body weight. On the basis of these findings a VSD (i.e. based on 1 x 10^{-6}) of 0.26 µ g/kg body weight was determined.

Remarkable agreement was noted between methods 1 and 3 and based on these results the maximum tolerable daily intake of ethyl carbamate in humans was estimated to be 0.3 µg/kg body weight."

These risk estimations appear unsatisfactory. The use of mathematical curve-fitting models has no basis in biology, and the risk estimates resulting from this approach differ by up to thirteen orders of magnitude, which leaves regulatory authorities with the task of making an arbitrary decision as to which of these very divergent estimates is the most appropriate in predicting risk to humans. The Canadian approach has produced a useable estimate, but seems to lack intellectual justification. The NOEL/safety margin approach (Method 1) employs an arbitrary safety factor of 5000, while the TD extrapolation approach (Method 3) assumes that the dose-response curve for carcinogenesis is linear: this is of course an arbitrary assumption.

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GUIDE TO THE CONSUMER PROTECTION ACT 1987

Product Liability and Safety Provisions

Department of Trade and Industry

This guide explains in general terms how the safety and product liability sections of the Consumer Protection Act 1987 will work. This is not a legal document and it does not attempt to cover all the details. Anyone who wants to know exactly how the Act will affect them should refer to the Act itself and possibly seek legal advice.

The Consumer Protection Act 1987 received Royal Assent on 15 May 1987. The product liability provisions come into force on 1 March 1988 and the general safety requirement on 1 October 1987. Part II of the Act (consumer safety, including the general safety requirement) applies throughout the United Kingdom. Part I (product liability) does not extend to Northern Ireland, but equivalent provision will be made for Northern Ireland by Order in Council. Copies of the Act can be obtained from Her Majesty's Stationery Office.

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FOREWORD

Every day of our lives we consume, use, or simply come into contact with countless different products. We should be able to assume that those products are safe. Not absolutely safe – that remains unattainable. Nor safe at unbearable cost to industry – that would put innovation at risk. But as safe as is reasonable to expect. The new Consumer Protection Act is a major step forward in safeguarding the consumer from products that do not reach a reasonable level of safety.

Clearly the consumer gains from this legislation. But forward-looking firms will also recognise that it is in their interest to outlaw unfair competition from traders who cut corners on safety. The Act is important to all those with an interest in the safety of products that are put onto the market.

I hope that businessmen and women will find this guide to the Act helpful in understanding the way in which it will work.

Francis Maude MP
Parliamentary Under Secretary of State for Corporate and Consumer Affairs
Department of Trade and Industry

PRODUCT LIABILITY

What does it mean?

1. People injured by defective products may have the right to sue for damages; product liability is the term given to laws affecting those rights.

2. In the past those injured had to to prove a manufacturer negligent before they could successfully sue for damages. The Consumer Protection Act 1987 removes the need to prove negligence. A customer can already sue a supplier, without proof of negligence, under the sale of goods law. The Act provides the same rights to anyone injured by a defective product, whether or not the product was sold to them.

3. The Act does not affect any existing civil laws governing product liability. No liability is imposed under the Act in respect of products first supplied before 1 March 1988.

4. The Act implements the European Community directive on product liability, which provides a similar degree of protection for people throughout the European Community.

Who is liable?

5. An injured person can take action against:-

Producers: usually the manufacturer, or in the case of raw materials the person who mined or otherwise obtained it. Also included are processors (for example pea canners), but those involved solely in packaging are not affected unless the packaging alters the essential characteristics of the product.

Importers: meaning importers into the European Community, not just into the United Kingdom. Where goods are imported into another EC country and subsequently sold in the United Kingdom, liability rests with the first importer, not the United Kingdom importer.

Own-branders: suppliers who put their own name on the product and give the impression that they are the producers.

6. Other suppliers, such as wholesalers and retailers, are not liable unless they fail to identify the producer, importer or "own-brander" if asked to do so by a person suffering damage.

7. Liability under the Act is joint and several, the plaintiff may sue both (or all, if more than two) defendants. It is not possible to exclude liability under the Act by means of any contract term or other provision.

What products are covered?

8. Liability under this part of the Act is not restricted to consumer goods. Unprocessed agricultural products are specifically excluded but all other goods, including those used at a place of work, are included.

9. Buildings are not covered although individual goods from which they are built (eg bricks and beams) are covered.

10. Liability under the Act extends to components and raw materials. If a finished product contains a defect in a particular component, both the manufacturer of the finished product and the component manufacturer may be liable.

11. The Act is not intended to extend to pure information. Printed matter is not therefore covered, except in the case of instructions or warnings for a product (in which case the producer of the *product* – not the printer – will be liable for errors or omissions in the instructions or warnings which make the product unsafe). Similarly, a design consultant will not be liable under the Act for a mistake in a design which causes a product to be defective; the producer of the product itself will be liable. Similar considerations are relevant to software. Computer software is often supplied

as an intrinsic part of a product and in some cases can cause personal injury (for example airline navigation systems or production line robots). Again, liability in such cases is imposed on the producer of the product.

What is a defective product?

12. A defective product is defined as one where the *safety* of the product is not such as persons generally are entitled to expect. This definition provides an objective test of defective and refers neither to the particular injured person nor to the particular producer. A product will not be considered defective solely because it is of poor quality. A product will not be considered defective simply because a safer version is subsequently put on the market.

13. When deciding whether a product is defective, a court will take into account all the relevant circumstances including –

the manner in which a product is marketed;

any instructions or warnings that are given with it;

what might reasonably be expected to be done with it;

the time the producer supplied the product.

14. The criteria of what might reasonably be expected to be done with a product, and consequently what instructions and warnings are given, is particularly important for producers and importers whose products are often misused.

What sort of damage is covered?

15. A person can sue under the Act for compensation for –

- death
- personal injury
- private property valued above $275.

16. The plaintiff must be able to show that, on the balance of probabilities, the defect in the product, caused the damage.

What defences are there?

17. A producer or importer can avoid liability if he can prove any of six defences:-

- ☐ he did not supply the product (eg it was stolen or is a counterfeit copy of his products);
- ☐ the state of scientific and technical knowledge at the time he supplied the product was not such that a producer of products of the same description as the product in question might be expected to have discovered the defect if it had existed in his products while they were under his control (the so-called "development risks defence");
- ☐ the defect was caused by complying with the law. Compliance with a regulation will not necessarily discharge a producer from liability; in order to claim the defence he would have to show that the defect was the *inevitable* result of compliance;
- ☐ the defect was not in the product at the time it was supplied (eg if a product becomes defective because a retailer handles it carelessly);
- ☐ the supplier is not in business. This excludes sales of home made toys to the church bazaar and sales by private individuals of secondhand goods;
- ☐ the producer of a component will not be liable if he is able to show that the defect was due either to the design of the finished product, or to defective specifications given to the component manufacturer by the producer of the finished product.

18. The extent of the defendant's liability could be affected by any contributory negligence on the part of the plaintiff, eg if he contributed to his injuries by his own carelessness.

When can injured people sue?

19. A plaintiff must begin his court action within three years of being injured by the defective product. An injured person cannot sue under this part of the Act ten years after the defective product was supplied by the producer.

THE GENERAL SAFETY REQUIREMENT

What does it mean?

20. From 1 October 1987 it will be a criminal offence to supply unsafe consumer goods in the United Kingdom. The Act provides that –

> a person shall be guilty of an offence if he supplies consumer goods which are not reasonably safe having regard to all the circumstances.

21. As at present, the safety of a range of consumer goods will continue to be controlled by regulations setting out in detail how specific types of goods must be constructed and what instructions and warnings must accompany them. It is not practical or desirable to make such regulations for every type of consumer product; the general safety requirement therefore closes a gap in the existing safety legislation.

22. As with safety regulations an offence may have been committed even when nobody has been injured.

23. Contravention of the general safety requirement can result in a fine not exceeding £2000, up to six months imprisonment, or both.

Who does it apply to?

24. Unlike the product liability provisions, the general safety requirement applies to *anyone who supplies the goods* although there is an important defence for retailers – that they neither knew nor had reasonable grounds for believing that the goods failed to comply with the general requirement.

What goods are covered?

25. This part of the Act is restricted to *consumer goods*. Some consumer goods are, however, not covered by the general requirement, for example growing crops, water, food, aircraft, motor vehicles, controlled drugs, medicinal products and tobacco.

What is a 'safe' product?

26. Safe is defined in the Act as reducing to a minimum the risk of death or personal injury.

27. The general safety requirement refers to goods being reasonably safe having regard to all the circumstances. These circumstances include –

the manner in which the goods are marketed and any instructions or warnings given with the goods;

any published safety standards for those goods; and

the means, if any, and the cost of making the goods safer.

What defences are there?

28. A supplier whose goods do not or may not meet the general safety requirement will still not be committing an offence if he can prove one of the following defences –

the goods conform *in a relevant respect* with a European Community obligation;

the goods conform to any applicable safety regulations or safety standards approved by the Secretary of State for Trade and Industry for the purpose of the general safety requirement;

the goods were for export;

the goods were not supplied as new and were not supplied by way of hire (ie the general safety requirement does not apply to the *sale* of secondhand goods);

for retailers, when the goods were supplied in the course of retail business he had no grounds for suspecting that the goods failed to comply with the general safety requirement.

STANDARDS

29. The general safety requirement is closely linked to standards. As already explained, any relevant standards will be among the circumstances to be considered in deciding whether goods are safe.

30. For greater certainty, some safety standards will be set by the Government as benchmarks of the general requirement. Goods which provide a level of safety equivalent to that of the relevant standard by some other means, will also satisfy the general requirement.

31. A comprehensive range of standards, mostly British but some international or foreign, will be approved by the Secretary of State. Compliance with an approved standard will ensure that goods also comply with the general safety requirement. A list of approved standards will be published from time to time and will be available for inspection at the Department of Trade and Industry.

32. Goods which meet an approved standard will satisfy the general safety requirement in respect of hazards covered by that standard. For any other hazards, outside the scope of the approved standard, the goods must be reasonably safe having regard to all the circumstances.

SAFETY REGULATIONS

33. The Act consolidates and improves the regulation-making powers available under previous consumer safety law. It also enables the Secretary of State to make regulations without delay where he considers it necessary on grounds of public protection.

34. The Act retains powers for the Secretary of State to make prohibition notices preventing named suppliers from supplying particular unsafe goods. It also provides powers for the Secretary of State to serve notices to warn, requiring named suppliers to publish warnings, at their own expense, about unsafe goods they have supplied.

ENFORCEMENT

35. As with previous safety legislation, enforcement of the safety provisions of the Act is primarily the responsibility of trading standards officers of local authorities. The Act increases their powers, which include the authority to make test purchases, and limited powers to enter and search premises and obtain information.

36. They can also issue suspension notices prohibiting suppliers from selling goods which they believe contravene safety legislation. They can apply to a magistrates' court for an order that such goods be forfeited and destroyed.

37. Producers and importers can appeal against suspension and forfeiture of goods; and apply for compensation for the cost imposed on them in certain circumstances. Customs Officers are empowered to detain goods at the port of entry for up to two working days to allow the enforcement authorities time to make initial enquiries about the safety of the goods detained.

WHAT BUSINESSES NEED TO DO

38. The vast majority of firms in this country already monitor and control the safety of the products they supply. The Consumer Protection Act provides an additional incentive for businesses to ensure that their products provide the safety that people using them or affected by them are reasonably entitled to expect. Use of the following checklist may help businesses to ensure that they meet their obligations under the new law –

review management procedures to check that all stages of production (design, manufacture, presentation and marketing) help to ensure that only safe products reach the customer;

check whether existing or proposed safety standards (whether approved for the general safety duty or not) are applicable and to what extent the firm's products are or could be made to meet the standard;

consider introducing a new quality assurance system. The UK has a national standard for managing the quality of manufacturing procedures. BS 5750 sets out how companies can establish, document and maintain an effective and economic system for developing and maintaining the quality of their products. When a firm has adopted BS 5750 it is then important to have the system independently checked and certified by a competent organisation;

assess whether the business's insurance cover is adequate, including product liability insurance. The amount of insurance cover obtained is a matter for commercial judgement, but businesses should seek advice from their own insurance advisors;

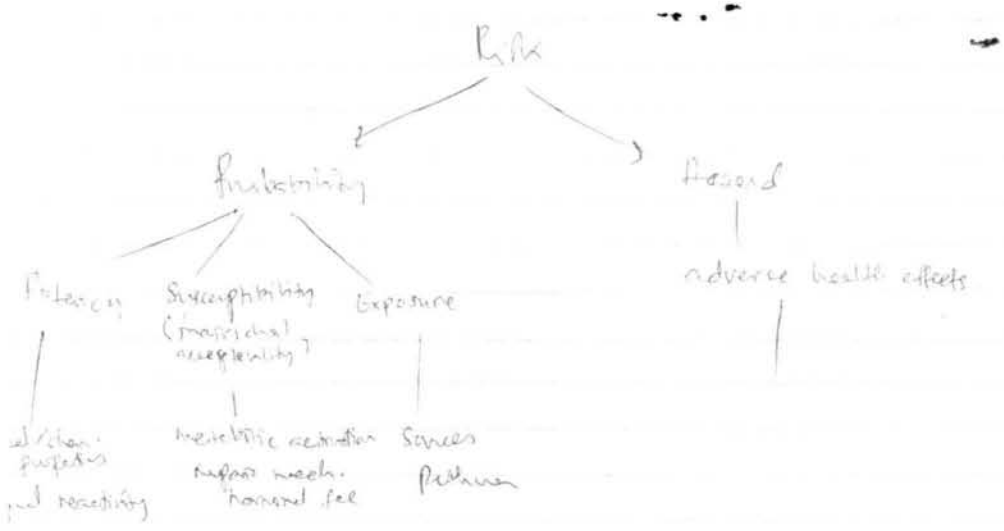
review any contractual arrangements with suppliers, customers or others with whom the business has relevant contracts (a business cannot contract out of any liability under the Act, but might, for example, seek an indemnity from others in the event of liability under the Act);

decide whether the records kept by the business are adequate, bearing in mind the working life of the product, the 10 year potential liability for product liability claims, and the possible need to identify suppliers of defective products to the business in defending a product liability action (particularly relevant for "own branders");

Additional information on consumer safety and on the Consumer Protection Act 1987 can be obtained from:

Consumer Safety Unit
Department of Trade and Industry
10-18 Victoria Street
London SW1H 0NN

Risk



Source
↓
transport & fate
↓
exposure (become concept in one sys.) ← become at the contact between a pollutant & the outer surface of the human body. exposure in term of cause of pollution
↓
uptake/metabolism
↓
dose

Type	Exp
(instantaneous) short duration, repeated long duration, continuous	occupational exposure, food consumption, drinking water

multi-media approach

Route of exp.

Human: skin, epithelial lining of respiratory and digestive tract.

Non-human: digestive tract and gills (fish) skin and leaves of aquatic.

Intake
↓
exposure
↓
uptake
↓
transport / metabolism
↓
dose

exposure ——→ dose
↓
measured in term of conc. at the site of eff. (cell, tissue, organ, whole organism).

Approaches

— modeling
— monitoring

eg: transport

models : air dispersion
aquatic transport
food chain
chem. transformation / speciation

monitoring : measurement of conc. and fluxes

-- (model & monitoring are mutually supportive)

#

Monitoring —— env. monitoring → ambient air, water bodies, food crops
—— exposure monitoring

↓

(human)

air : indoor / ant door
water : drinking water (at the tap)
food : as consumed
lifestyle : occupation, consumer products smoking

#

- site selection
- frequency of sampling
- sampling method
- preservation of samples
- analytical method
- reporting and interpretation of result

Biomarker

Biological monitoring

— analysis of biological specimens (blood, excreta)
— measurement of biological response (enzyme activity)

est of nth to human health.

- Eff on [illegible] : epidemiology
- Eff on animal : toxicity
- Eff on other species in their ecosystem
- Structural relationships

Sources of information on effect of nth

- epidemiological study
- toxicological expts
- In vitro
- structural / computing

① epidemiology

② toxicity expts using animal

- acute toxicity study
- metabolism and pharmacokinetics

③ In vitro test

④ Structural / computer

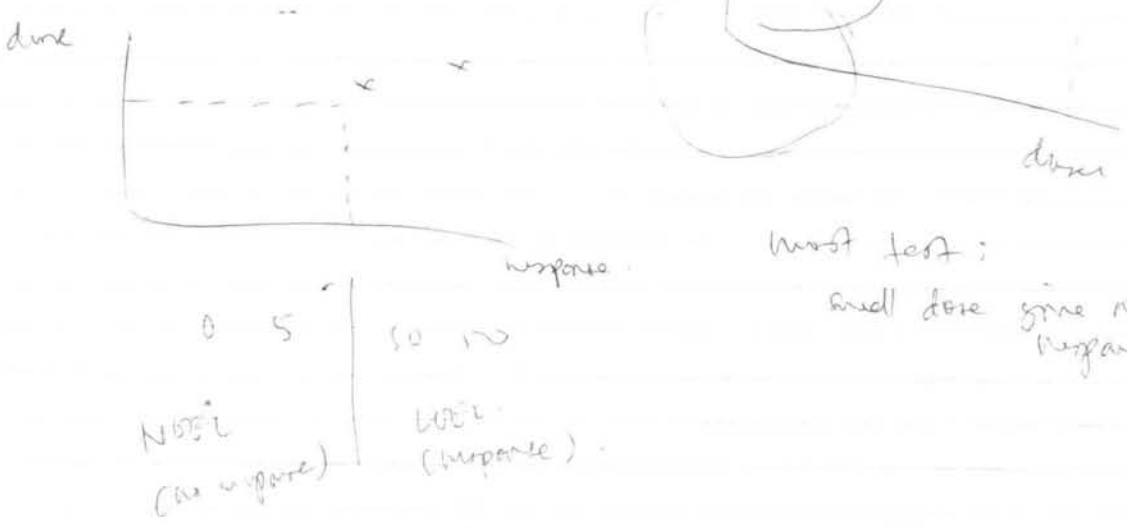
Exposure.

ADI = NOEL / SF

acceptable daily intake

No observed eff. level

Safety factor



Worst test:
small dose give no response.

0 5	50 100
NOEL (no response)	LOEL (response)

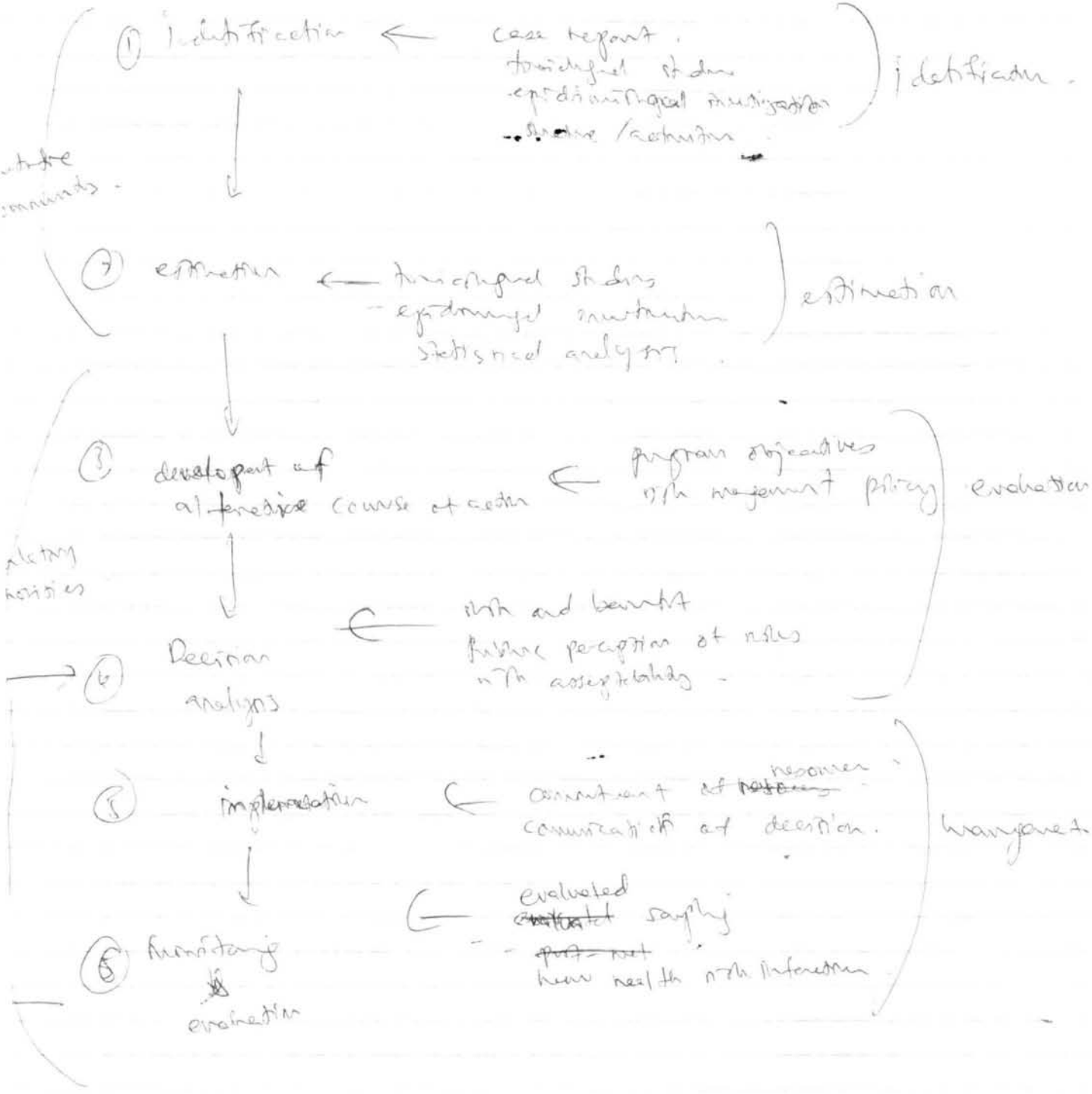
potency = 7 − log (TD_{50})

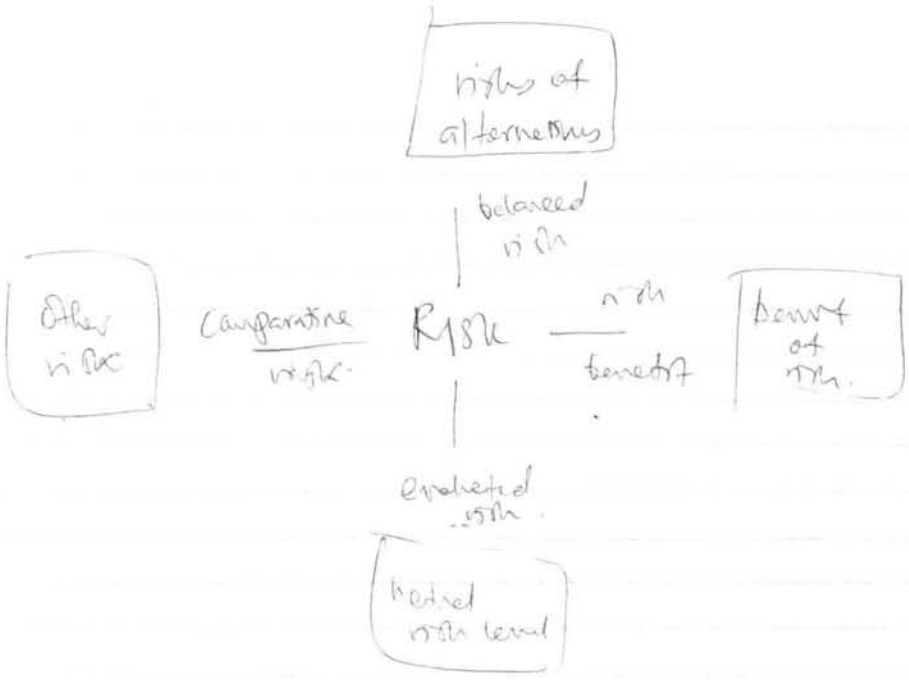
Weighted contribution

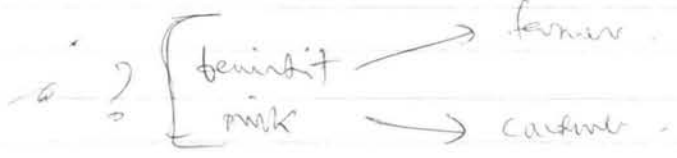
- no of species and strains affected.
- no of tissues or site at which tumors occur
- latency period
- strength of dose req. to reduce tumor.
- proportion of benign and malignant lesion.
- nature & degree of other pathological change.
- weighted correlation with DNA
- genotoxicity.

Steps in risk ass.

- risk identification
- risk estimation
- risk evaluation
- risk management.


1 identification
case report
toxicological studies
epidemiological investigation
identification
estimation
program objectives
risk management policy
evaluation
risk and benefit
future perception of risks
risk acceptability
Decision analysis
implementation
communication of decision
management
evaluated
quality
monitoring
evaluation


risks of alternatives
balanced risk
Other risk
Comparative risk
Risk
risk
benefit
Amount of risk
Evaluated risk
Retired risk level


benefit
risk
former
current

REGULATIONS MADE UNDER THE CONSUMER PROTECTION ACT 1961

SUBJECT	STATUTORY INSTRUMENT NO:
The Stands for Carry Cots (Safety) Regulations 1966	SI 1610
The Toys (Safety) Regulations 1974	SI 1367
The Electrical Appliances (Colour Code) Regulations 1969, 1970 and 1977	SI 310, 811 and 931
The Electric Blankets (Safety) Regulations 1971	SI 1961
The Cooking Utensils (Safety) Regulations 1972	SI 1957
The Heating Appliances (Fireguards) Regulations 1973	SI 2106
The Pencils and Graphic Instruments (Safety) Regulations 1974	SI 226
The Glazed Ceramic Ware (Safety) Regulations 1975	SI 1241
The Electrical Equipment (Safety) Regulations 1975 and 1976	SI 1366 and 1208
The Vitreous Enamel-Ware (Safety) Regulations 1976	SI 454
The Children's Clothing (Hood Cords) Regulations 1976	SI 2
The Oil Heaters (Safety) Regulations 1977	SI 167
The Babies' Dummies (Safety) Regulations 1978	SI 836
The Cosmetic Products Regulations 1978 **	SI 1354
The Perambulators and Pushchairs (Safety) Regulations 1978	SI 1372
The Oil Lamps (Safety) Regulations 1979	SI 1125
The Cosmetic Products (Amendment) Regulations 1983 **	SI 1477
The Aerosol Dispensers (EEC requirements) and the Cosmetic Products (Amendment) Regulations 1985 **	SI 1279

REGULATIONS MADE UNDER CONSUMER SAFETY ACT 1978

The Dangerous Substances and Preparations (Safety) Regulations 1980 **	SI 136
The Upholstered Furniture (Safety) Regulations 1980	SI 725
The Novelties (Safety) Regulations 1980	SI 958
The Filament Lamps for Vehicles (Safety) Regulations 1982 *	SI 444
The Upholstered Furniture (Safety) (Amendment) Regulations 1983	SI 519
The Pedal Bicycles (Safety) Regulations 1984*	SI 145
The Motor Vehicle Tyres (Safety) Regulations 1984 *	SI 1233
The Cosmetic Products (Safety) Regulations 1984 **	SI 1260
The Gas Catalytic Heaters (Safety) Regulations 1984	SI 1802
The Food Imitations (Safety) Regulations 1985	SI 99
The Dangerous Substances and Preparations (Safety) (Amendment) Regulations 1985	SI 127
The Novelties (Safety) (Amendment) Regulations 1985	SI 128
The Food Imitations (Safety) (Amendment) Regulations 1985	SI 1191
The Asbestos Products (Safety) Regulations 1985 **	SI 2042
The Nightwear (Safety) Regulations 1985	SI 2043
The Cosmetic Products (Safety) (Amendment) Regulations 1985 **	SI 2045
The Pushchairs (Safety) Regulations 1985	SI 2047
The Child Resistant Packaging (Safety) Regulations 1986	SI 758
The Fireworks (Safety) Regulations 1986	SI 1323
The Nightwear (Safety) (Amendment) Regulations 1987	SI 286

The Plug and Socket etc (Safety) Regulations 1987	SI 603
The Bunk Beds (Entrapment Hazards) (Safety) Regulations 1987	SI 1337

PROHIBITION NOTICES MADE UNDER THE CONSUMER SAFETY ACT 1978

Automatic Electric Rice Cooker made 26 January 1983

Sprint 0.6 TA Scissor Car Jack made 11 October 1984

Expanding Novelties known as New Grobots, New Grobugs and New Grobeasts made 20 November 1985

PROHIBITION ORDERS MADE UNDER THE CONSUMER SAFETY ACT 1978-ALL NOW EXPIRED

The Nightwear (Safety) Order 1978	SI 1728
The Balloon-Making Compounds (Safety) Order 1979	SI 44
The Tear Gas Capsules (Safety) Order 1979	SI 887
The Children's Furniture (Safety) Order 1982	SI 523
The Toy Water Snakes (Safety) Order 1983	SI 1366
The Gas Catalytic Heaters (Safety) Order 1983	SI 1696
The Expanding Novelties (Safety) Order 1983	SI 1791
The Scented Erasers (Safety) Order 1984	SI 83

OTHER REGULATIONS

The Packaging and Labelling of Dangerous Substances Regulations 1978 ***	SI 209
The Packaging and Labelling of Dangerous Substances (Amendment) Regulations 1981	SI 792
The Packaging and Labelling of Dangerous Substances (Amendment) Regulations 1983	SI 17
The Aerosol Dispensers (EEC Requirements) Regulations 1977 (Made under the European Communities Act 1972)	SI 1140
The Aerosol Dispensers (EEC Requirements) (Amendment) Regulations 1981	SI 1549
The Fabrics (Misdescription) Regulations 1959 ****	SI 616
The Fabrics (Misdescription) Regulations 1980 ****	SI 726
The Classification Packaging and Labelling of Dangerous Substances Regulations 1984 ***	SI 1244
The Classification Packaging and Labelling of Dangerous Substances (Amendment) Regulations 1986 ***	SI 1922

* Regulations made by the Department of Transport

** Also uses powers under EC Act 1972

*** Made jointly by this Department and the Department of Employment under the Health and Safety at Work etc Act 1974, and the European Communities Act 1972

**** Made under the Fabrics Misdescription Act 1913

Problems for Discussion

1. Should the United Kingdom prohibit the export of goods whose sale is prohibited in the UK by Regulations as unsafe?

2. It is an offence in the UK to sell products that are unsafe by UK standards. Should this be applied to exports?

3. Do the public have the right to know the active ingredients of a product if they are a commercial secret?

4. Should non-food products carry a list of all ingredients?

5. Should it be an offence to sell unsafe secondhand goods by way of business?

6. Should there be a "development risks" defence for new products in the law on product liability ie that the manufacturer could not have been expected to know at the time that a product would turn out to be dangerous?

7. Primary agricultural products are exempt from strict product liability. Is this right?

8. Does the public have the right to know that a product is for example radio-active if it has been properly approved as safe?

R J Roscoe
DTI/CSU
22 October 1987.

11/12 87 13.00 6.00 12.00 11/12. Dr. Ahmad.

D Gree.

15.00 h 12 m

Dr. Johan Sohaili

DGree — Chemical Risks.

(1). Approach to question.
(2). Summary the existing laws / Act — Canada
(3). Examples of material can cause risk.

T.U approach to toxic sub.
1. assume harmful, not harmless
2. consider all evidences
   - structural
   - biochemical
   - animal
   - human — worker's experience
     - epidemiological
3. How weigh to positive / negative evidence.
4. Lower level of proof balance of probabilities, not beyond all

Decision makers.

Course assessment.
Course assessment
Cour
Course.

Course Assessment.

Jean
DSE (Mal)
11/12/87 (London

THE INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

AN OVERVIEW

by Dr E. Smith

November 1987

Sohaili / Johan Mr.

Introduction

Chemicals are essential for producing and sustaining national development. They are of major importance in virtually every industry, and have a key role in preventing and controlling disease, increasing agricultural productivity and facilitating food storage and preservation. While chemicals have brought many benefits they have also had negative effects on human health and on the integrity of the environment, notably when they are produced, used and disposed of carelessly and indiscriminately.

The safe production, use and disposal of chemicals is often seen, mistakenly, as a problem confined to the developed industrialized countries. However, the growing production of chemicals in the developing countries and the ever-increasing international trade means that all countries are now either producers, formulators or users of chemicals and are exposed to the possibility of adverse effects. Chemical safety is relevant to all, from national authorities to individuals, because all are exposed to chemicals in the home, the workplace and the natural environment.

The primary purpose of chemical safety is to ensure that exposure to chemicals, natural as well as synthetic, does not harm humans or the environment. This is not only to avoid the dramatic effects of acute poisoning but also to prevent the possible insidious effects of long-term low-level exposures of large populations.

A large number of chemicals is available commercially with, for example, around 70,000 listed in the US Toxic Substances Control Act inventory and 100,000 in the European Economic Community's list. However, the volumes of production and use, and the range of uses vary widely. The number of mixtures and formulations in use worldwide is many times greater.

The number, type and quantities of chemicals used in countries vary widely according to factors such as the national economy, its industrial base and the extent of agriculture. The productivity, ingenuity and competitiveness of chemical industries are noteworthy and innovation is vigorously pursued. Thousands of chemicals are synthesized experimentally each year to determine if they offer advantages over their predecessors and are viable commercially. Of this number, probably over 1,000 enter commerce. The chemical scenario is constantly changing because new chemicals and formulations come on the market, older ones are superseded by better alternatives, and the quantities produced and used vary with demand.

Development of the International Programme on Chemical Safety (IPCS)

The IPCS is a cooperative programme of the United Nations Environment Programme (UNEP), the International Labour Office (ILO), and the World Health Organization (WHO). WHO is the executing agency for the programme and the Central Unit of the IPCS is located in the WHO Division of Environmental Health in Geneva, Switzerland.

In 1972 the United Nations Conference on the Human Environment took place in Stockholm, Sweden. There was intense international concern about the dangers of chemicals for humanity and the natural environment. This conference recommended that programmes, to be guided by WHO, should be undertaken for the

early warning and prevention of the harmful effects of the various environmental agents, acting singly or in combination, to which humans were being increasingly exposed, directly and indirectly, and for the assessment of the potential risks for human health.

As the Specialized Agency for Health in the United Nations system, WHO has a mandate from its Member States to address all the factors which have an impact on human health and this includes chemicals. WHO is striving for Health for All by the Year 2000, based on balanced social and economic development, with health both a result of, and a key factor in, this development.

In 1977 the World Health Assembly requested the Director-General to study the problem of long-term strategies to control and limit the impact of chemicals on human health and the environment. On this basis a programme was developed and structured by WHO. The interest of other international organizations in chemical safety was clearly demonstrated by ILO and UNEP joining with WHO in the IPCS which was formally launched in 1980 when a Memorandum of Understanding (MOU) was signed between the three organizations.

Objectives of the IPCS

The objectives are to catalyse and coordinate activities in relation to chemical safety, and in particular to:

(i) carry out and disseminate evaluations of the risk to human health and the environment from exposure to chemicals, mixtures of chemicals or combinations of chemicals and physical and biological agents;

(ii) promote the development, improvement, validation, and use of methods for laboratory testing and ecological and epidemiological studies and other methods suitable for the evaluation of health and environmental risks and hazards from chemicals;

(iii) promote technical cooperation with Member States, in particular developing countries to:

(a) facilitate the use of available evaluations of health and environmental risks and hazards from chemicals;

(b) improve the capabilities of national authorities in conducting their own evaluations of health and environmental risks and hazards from chemicals;

(c) strengthen infrastructures for safety aspects relating to chemicals - their production, importation, transportation, storage, use, and disposal;

(iv) promote effective international cooperation with respect to emergencies and accidents involving chemicals;

(v) support national programmes for prevention and treatment of poisonings involving chemicals;

(vi) promote training of the required manpower.

In order to ensure efficient use of resources and integration of the results the IPCS works closely with other international and WHO programmes which are also involved in the area of safe use of chemicals. Examples are collaboration with the Council for Mutual Economic Assistance (CMEA), the Organization for Economic Research and Development (OECD), the Commission of the European Communities (CEC) and the WHO programmes on environmental pollution, occupational health, safe use of pesticides and food safety. There is close collaboration with the Food and Agriculture Organization (FAO) for the joint safety evaluations of food additives, pesticide residues in food and veterinary drug residues in meat.

Activities and Outputs of the IPCS

For each objective there are outputs. These include the worldwide dissemination of information and publications directed to a wide range of readers, meetings of international experts and training courses for students from many countries.

Publications on Risk Assessment

Environmental Health Criteria (EHC) Documents

This series covers evaluations of specific chemicals or groups of chemicals, monographs dealing with methodology and monographs on physical hazards.

Seventy-three EHC documents have been published, two are in press, and thirty-nine are in various stages of preparation. Of those published there are fifty-five monographs on chemicals, ten on methodology and eight on physical hazards. These documents, prepared in collaboration with experts from all parts of the world, review and evaluate current knowledge and provide a basis for assessment of hazards.

Priority chemicals for assessment by IPCS and publication as EHCs are identified with the participation of international experts and in collaboration with IARC, IRPTC and allied WHO programmes. A new list has recently been prepared based on inputs from international bodies, governments and industries using broad selection criteria such as quantity of production, types and extent of uses, toxicity, ecotoxicity and environmental persistence.

IPCS publications are disseminated widely to international organizations, national authorities, and scientific and industrial associations to provide a basis for chemical safety planning and for the development and implementation of control measures. The documents are available in English and French and many have been translated into other languages.

Health and Safety Guides (HSGs)

To make information on chemicals more widely available these booklets have been designed to meet the needs of a wide range of administrators, managers and decision-makers in governmental ministries and agencies, and in commercial and industrial undertakings to enable them to achieve chemical safety and avoid human and environmental health hazards. Health and Safety Guides are short

documents summarizing in simple, non-technical language the relevant physical and chemical properties and evaluated information on toxicity and ecotoxicity. They give practical advice on safe storage, handling and disposal, accident prevention, and human health and environmental protection measures. First aid and medical treatment in cases of human exposure and clean-up procedures for environmental contamination are important sections for handling emergencies. HSGs also give information on permitted occupational exposure levels and other limits for a range of countries. The aim is to keep these booklets concise and use a simple style and presentation to ensure that the advice is easy to read, understand and apply. Simplicity of text facilitates translation into other languages. To date, eleven HSGs have either been published or are in press. HSGs for another fifty-four chemicals will be produced in 1988-89. HSGs are prepared routinely for all the chemicals reviewed and evaluated in EHCs.

International Chemical Safety Cards (ICSCs)

These are being developed to provide a simple summary of essential identity data and health and safety information on a card (or poster). They are designed for use by people who use chemicals in their work or may be involved with them in storage and transportation. The cards also provide useful information to people involved in handling cases of poisoning such as "first-aiders", workplace safety officers, police, firemen, para-medical personnel, and primary health care workers. A standard format for the cards will ensure wide acceptability, easy use and facilitate translation into many languages. It is planned to publish ICSCs on 400 chemicals in 1988-89.

Monographs on i) Food Additives and ii) Pesticide Residues in Food

In collaboration with FAO, the IPCS has evaluated or re-evaluated more than 200 food additives, food contaminants and growth-promoting agents in order to establish acceptable daily intakes. For pesticides, maximum residue levels in food have been set for 140 used extensively in agriculture and public health. Monographs are published annually and the evaluations provide information on toxicology and safe levels of exposure and assist governments in establishing permissible legal levels of these substances in foodstuffs. Veterinary drugs are now coming under similar scrutiny because their use can leave residues in meat and similar evaluations will be made by an expert advisory committee.

Development of Methodology

An important task of the IPCS is to foster the development of internationally accepted approaches and methods for testing, assessing and predicting the effects of chemicals on human health and the environment. In this context, human epidemiological studies linked with chemical exposure on a global level are important. Harmonization of test methods will facilitate comparability, general acceptance and use of data obtained in different countries and promote effective chemical safety. Harmonization is not just bringing national test methods closer together but is also directed to producing a better understanding of the philosophy and scientific basis for testing.

In this area IPCS works closely with intergovernmental organizations such as the Council for Mutual Economic Assistance (CMEA), the Commission of the European Communities (CEC), and the Organisation for Economic Cooperation and Development (OECD) and with scientific groups. This ensures coordination and avoids duplication of effort and waste of scarce resources. The involvement of IPCS contributes to the work of other organizations because it facilitates truly international understanding and agreement on the basic principles on which national requirements for testing and assessing chemicals for their toxic and ecotoxic effects can be based. A crucial part of the development of methodology is publication of monographs which provide a critical analysis of current test methods and approaches to predicting health and environmental risks. Better testing strategies for producing more reliable and comparable results are developed in these monographs.

Another important IPCS activity in the field of methodology is the organization , coordination and facilitation of inter-laboratory collaborative studies aimed at validating existing test methods, developing new methods and improving the interpretation of results. This is reserved for test areas where the international cooperation of scientific bodies and institutions is essential for the work to be carried out satisfactorily and meaningful results produced. Other intergovernmental and scientific organizations may collaborate with IPCS in these studies.

An outstanding feature of the development of methodology is the active participation of scientists from all over the world. This participation, and the interactions between individual scientists and institutions, contribute greatly to the harmonization of testing and risk assessment in the developing, industrializing countries as well as in the developed countries. An international approach to the principles and methodology of risk assessment is of particular benefit to countries where rapid industrialization and expansion of agriculture give rise to serious potential hazards from chemicals because their scientists normally have to use data and risk assessments generated elsewhere and apply them to their own national situation. Participation also directly contributes to the development of scientific and institutional expertise at national level.

Management of Chemical Emergencies

The large number and volume of chemicals extracted, manufactured, transported, marketed, stored, used and disposed of as wastes, constitute a significant risk of accidental exposure and poisoning. Accidents ranging from major catastrophes to minor leakages and spills occur frequently. More rational and effective approaches are needed to prevent, or where prevention fails, to tackle the consequences of chemical accidents in order to avoid damage to human health and the environment. At a practical level, IPCS is working with the World Federation of Clinical Toxicology Centres and Poison Control Centres to define the type of information and institutional capacity required for the treatment of poisoning and structured poison prevention and control programmes. The clinical diagnosis and treatment of poisoning is now a regular feature of EHC documents on chemicals and Health and Safety Guides. Special attention is given to specific antidotes and their use, although it must be recognized that these are available for relatively few chemicals; frequently, general supportive treatment is all that can be given. A primary aim is to make developing countries, whose populations experience a high proportion of poisoning by

chemicals, self sufficient in poison control and treatment. The training of manpower and production of teaching material is an important part of this activity.

Manpower Development in the Field of Chemical Safety

The capacity of countries to ensure the safe use of chemicals and to adapt to their needs toxicological and ecotoxicological data and risk assessments made elsewhere is conditioned by the availability of resources (financial, individual, institutional) and scientific and managerial expertise. Achieving chemical safety requires governmental initiative, trained manpower and an informed population. The IPCS gives high priority to manpower development and promotes training in understanding the nature of chemical hazards, the uses of toxicological and ecotoxicological test data, risk assessment and safe use of chemicals under a variety of conditions.

Training materials are prepared and courses and seminars are organized. Training materials and approaches to training must be adapted to meet the needs of different countries to make them self-reliant and able to manage their own chemical safety and training programmes. Workshops are organized to promote chemical safety, provide awareness of the practical uses of toxicology and ecotoxicology and stimulate the development of national programmes. The majority of training activities are funded and organized jointly with other international and national bodies. Activities organized with national authorities are especially valuable because they provide a firm foundation on which countries can develop and run their own courses.

Technical Cooperation

This is an integral part of all IPCS activities. In WHO technical cooperation is a primary responsability of Regional Offices. WHO is divided into six Regions. Each Region defines its priorities for health based on the conditions prevailing within its countries. Some Regions already have established programmes dealing with chemical safety and others are in the process of doing so. To deal with the increasingly complex health and environmental problems caused by the use of chemicals, it is obviously in the interest of all to share knowledge and resources. Scientific knowledge needs to be shared otherwise developing countries will not be able to achieve the expertise needed to tackle their problems. The IPCS has a key role because it is directed to international cooperation rather than isolated national efforts. Public demand for protection from chemical (and other) hazards is not unique to any country and assessments of risk and hazard provided by IPCS and its internationally recognized and independent experts have an important role to play in ensuring chemical safety worldwide.

ENVIRONMENTAL HEALTH CRITERIA SERIES

1.	Mercury	(1976)
2.	Polychlorinated Biphenyls and Terphenyls	(1976)
3.	Lead	(1977)
4.	Oxides of Nitrogen	(1977)
5.	Nitrates, Nitrites, and *N*-Nitroso Compounds	(1978)
6.*	Principles and Methods for Evaluating the Toxicity of Chemicals, Part 1	(1978)
7.	Photochemical Oxidants	(1978)
8.	Sulfur Oxides and Suspended Particulate Matter	(1979)
9.	DDT and its Derivatives	(1979)
10.	Carbon Disulfide	(1979)
11.	Mycotoxins	(1979)
12.	Noise	(1980)
13.	Carbon Monoxide	(1979)
14.	Ultraviolet Radiation	(1979)
15.	Tin and Organotin Compounds	(1980)
16.	Radiofrequency and Microwaves	(1981)
17.	Manganese	(1981)
18.	Arsenic	(1981)
19.	Hydrogen Sulfide	(1981)
20.	Selected Petroleum Products	(1982)
21.	Chlorine and Hydrogen Chloride	(1982)
22.	Ultrasound	(1982)
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24.	Titanium	(1982)
25.	Selected Radionuclides	(1983)
26.	Styrene	(1983)
27.*	Guidelines on Studies in Environmental Epidemiology	(1983)
28.	Acrylonitrile	(1983)
29.	2,4-Dichlorophenoxyacetic Acid (2,4-D)	(1984)
30.*	Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals during Pregnancy	(1984)
31.	Tetrachloroethylene	(1984)
32.	Methylene Chloride	(1984)
33.	Epichlorohydrin	(1984)
34.	Chlordane	(1984)
35.	Extremely Low Frequency (ELF) Fields	(1984)
36.	Fluorine and Fluorides	(1984)
37.	Aquatic (Marine and Freshwater) Biotoxins	(1984)
38.	Heptachlor	(1984)
39.	Paraquat and Diquat	(1984)

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* Methodology document (yellow cover).

40.	Endosulfan	(1984)
41.	Quintozene	(1984)
42.	Tecnazene	(1984)
43.	Chlordecone	(1984)
44.	Mirex	(1984)
45.	Camphechlor	(1984)
46.*	Guidelines for the Study of Genetic Effects in Human Populations	(1985)
47.*	Summary Report on the Evaluation of Short-Term Tests for Carcinogens (Collaborative Study on In Vitro Tests)	(1985)
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49.	Acrylamide	(1985)
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53.	Asbestos and Other Natural Mineral Fibres	(1986)
54.	Ammonia	(1986)
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56.	Propylene Oxide	(1985)
57.*	Principles of Toxicokinetic Studies	(1986)
58.	Selenium	(1986)
59.*	Principles for Evaluating Health Risks from Chemicals During Infancy and Early Childhood: The Need for a Special Approach	(1986)
60.*	Principles and Methods for the Assessment of Neurotoxicity Associated With Exposure to Chemicals	(1986)
61.	Chromium	(in press)
62.	1,2-Dichloroethane	(1987)
63.	Organophosphorus Insecticides - A General Introduction	(1986)
64.	Carbamate Pesticides - A General Introduction	(1986)
65.	Butanols - Four Isomers	(1987)
66.	Kelevan	(1986)
67.	Tetradifon	(1986)
68.	Hydrazine	(1987)
69.	Magnetic Fields	(1987)
70.*	Principles for the Safety Assessment of Food Additives and Contaminants in Food	(1987)
71.	Pentachlorophenol	(1987)
72.*	Principles of Studies on Diseases of Suspected Chemical Etiology and Their Prevention	(1987)

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* Methodology document (yellow cover).

73.	Phosphine and Metal Phosphides	(in press)
74.	Diaminotoluenes	(1987)
75.	Toluene Diisocyanates	(1987)
	Thiocarbamate Pesticides - A General Introduction	(in press)
	Dithiocarbamate Pesticides - A General Introduction	(in preparation)
	Dichlorvos	(in preparation)
	Cypermethrin	(in preparation)
	Pyrrolizidine Alkaloids	(in preparation)
	TCDD	(in preparation)
	Vanadium	(in preparation)
	Dimethoate	(in preparation)
	Aldrin and Dieldrin	(in preparation)
	Man-Made Mineral Fibres	(in preparation)
	Mycotoxins	(in preparation)
	Allethrins	(in preparation)
	Resmethrins	(in preparation)
	Tetramethrin	(in preparation)
	d-Phenothrin	(in preparation)
	Deltamethrin	(in preparation)
	Permethrin	(in preparation)
	Fenvalerate	(in preparation)
	1-Propanol	(in preparation)
	2-Propanol	(in preparation)
	Vinylidene Chloride	(in preparation)
	Formaldehyde	(in preparation)
	Dimethylformamide	(in preparation)
	Cadmium	(in preparation)
	Isobenzan	(in preparation)
	Propachlor	(in preparation)
	Chlorofluorocarbons	(in preparation)
	PCBs/PCTs	(in preparation)
	Phenol	(in preparation)
	Chlorobenzenes	(in preparation)
	Hexachlorobenzene	(in preparation)
	Chlorophenols	(in preparation)
	Aldicarb	(in preparation)
	Hexachlorocyclopentadiene	(in preparation)
	Photochemical Oxidants (Update)	(in preparation)
	Sulfur Oxides and Suspended Particulate Matter(2nd edition)	(in preparation)
	Selected Glycol Ethers	(in preparation)
	Phthallates	(in preparation)
	LAS	(in preparation)

HEALTH AND SAFETY GUIDE SERIES

Acrylonitrile	(1986)
Kelevan	(1987)
Methylene Chloride	(in press)
Tetrachloroethylene	(in press)
1-Butanol	(in press)
2-Butanol	(in press)
2,4-D	(in press)
Epichlorohydrin	(in press)
tert-Butanol	(in press)
Isobutanol	(in press)
Tetradifon	(in press)
Chlordane	(in preparation)
Hepatachlor	(in preparation)
Quintozene	(in preparation)
Tecnazene	(in preparation)
Endosulfan	(in preparation)
Ethylene Oxide	(in preparation)
Propylene Oxide	(in preparation)
Dimethoate	(in preparation)
Aldrin and Dieldrin	(in preparation)
Phosphorus Trichloride	(in preparation)
Phosphorus Oxychloride	(in preparation)
Phosphine	(in preparation)
Ammonia	(in preparation)
Dimethyl Sulfate	(in preparation)
Dichlorvos	(in preparation)
Cypermethrin	(in preparation)
Hydrazine	(in preparation)
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Fenvalerate	(in preparation)
1-Propanol	(in preparation)
2-Propanol	(in preparation)
Phenol	(in preparation)
Dimethylformamide	(in preparation)
Propachlor	(in preparation)
Isobenzan	(in preparation)

Endrin	(in preparation)
Xylenes	(in preparation)
Ethylbenzene	(in preparation)
Acetaldehyde	(in preparation)
Acroleine	(in preparation)
Hexachlorobutadiene	(in preparation)
Hexachlorocyclopentadiene	(in preparation)
Aldicarb	(in preparation)
Malathrin	(in preparation)
Fenitrothrin	(in preparation)
Trichlorfon	(in preparation)
Chlorophenols	(in preparation)
Chlorobenzenes	(in preparation)
Selected Glycol Ethers	(in preparation)

CHEMICAL SAFETY PROJECT in POLAND

Focal point
for the project: Nofer's Institute of Occupational Medicine, Łódź

Director: Professor J. A. Indulski

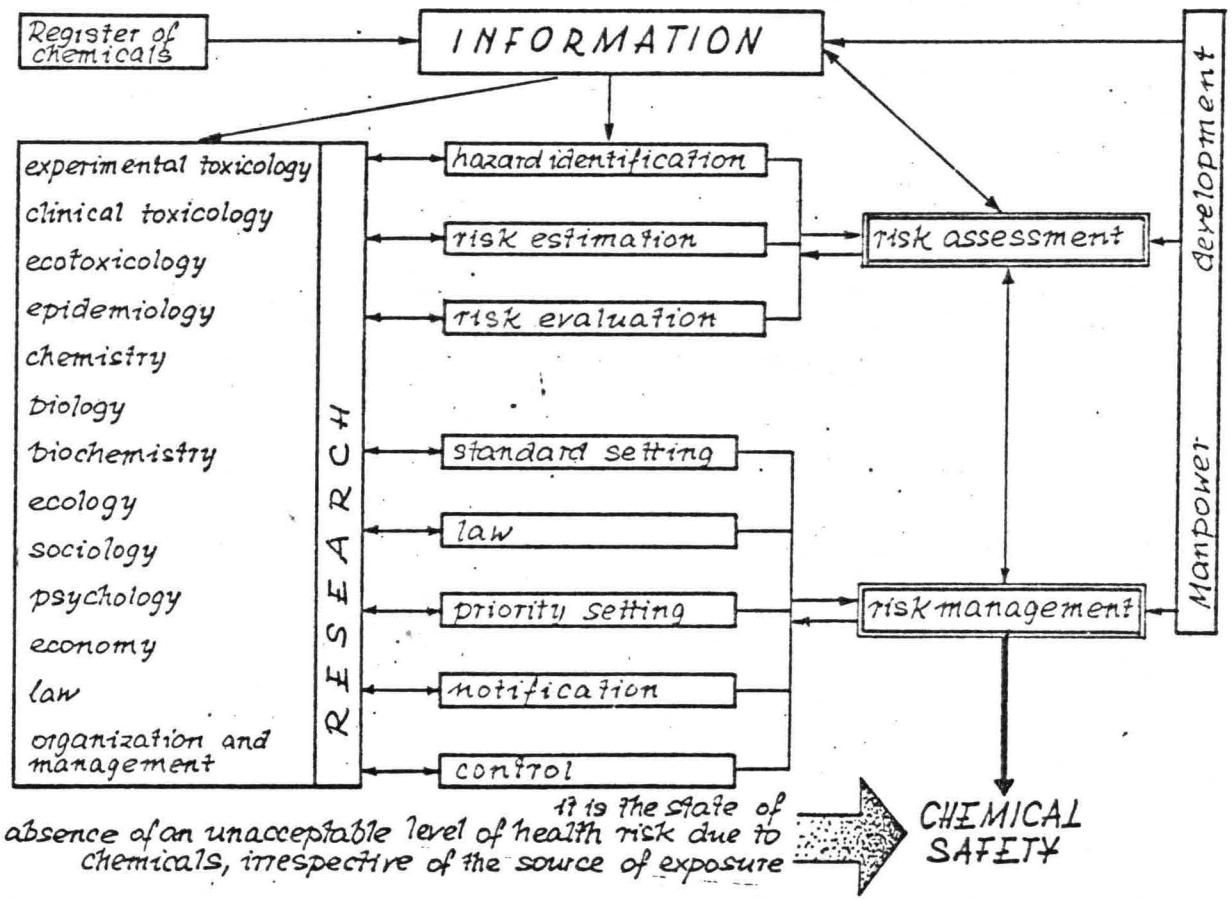
AIMS and OBJECTIVES

AIM of the PROJECT:
Initiation and coordination of activities for limiting health effects of human exposure to chemicals.

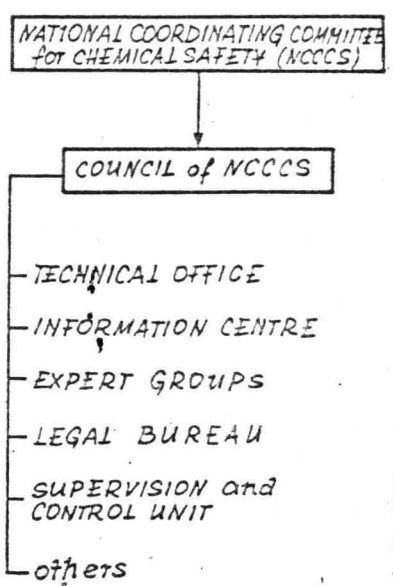
OBJECTIVES:

1) Evaluation of health risk arising from exposure to chemicals
2) Development of methods for exposure monitoring as well as epidemiological studies for risk assessment
3) Development of uniform methods of setting standards for chemical content in the air, water, food and consumer products
4) Implementation of chemical safety system
5) Establishment of National Coordinating Committee for Chemical safety
6) Setting priorities for chemical safety
7) Establishment of toxicological information system
8) Coordination of research on problems related to chemical safety
9) Manpower development and training for chemical safety
10) Development of international collaboration, especially within the framework of International Programme of Chemical Safety
11) Development of regulatory control system for chemical safety

FRAMEWORK



ORGANIZATIONAL SYSTEM
(under preparation)



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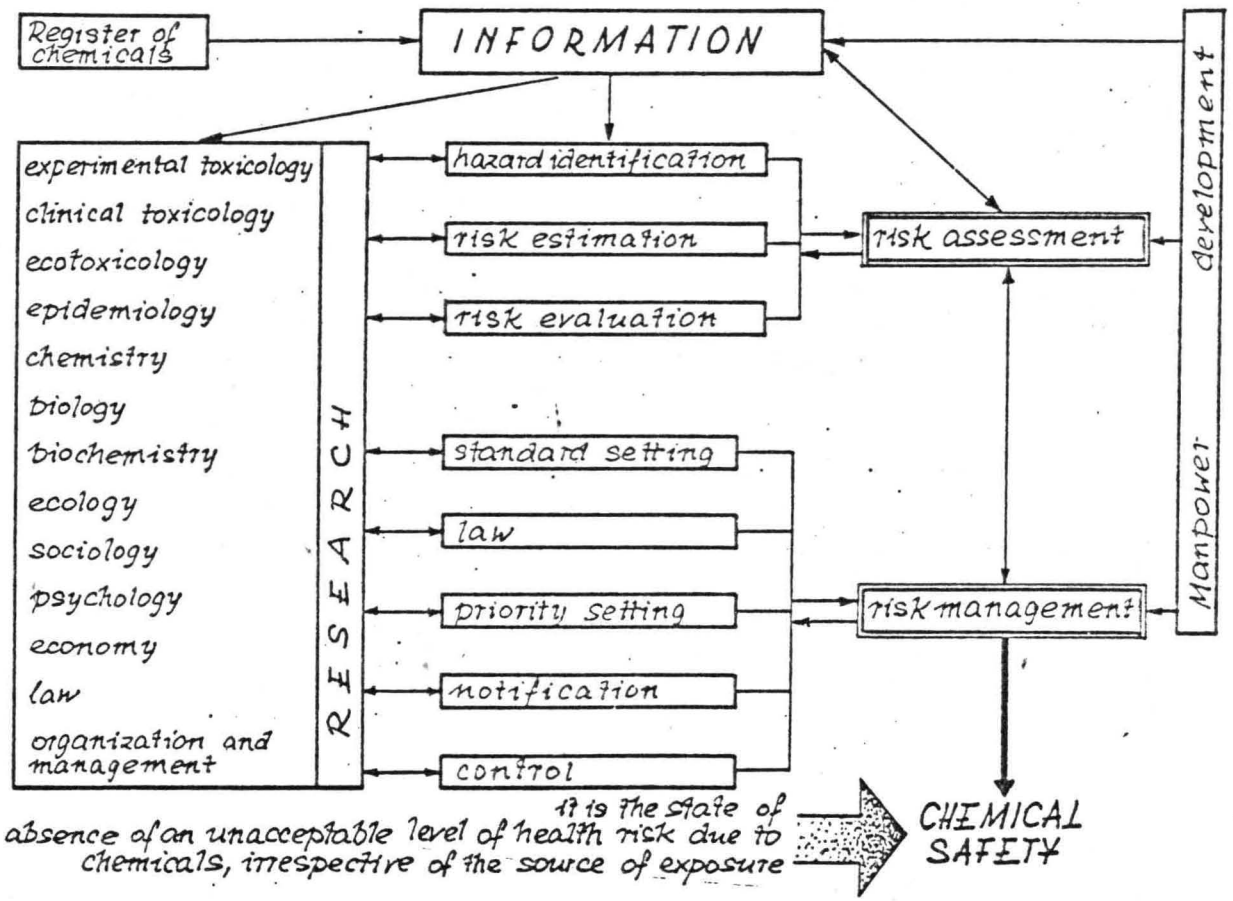

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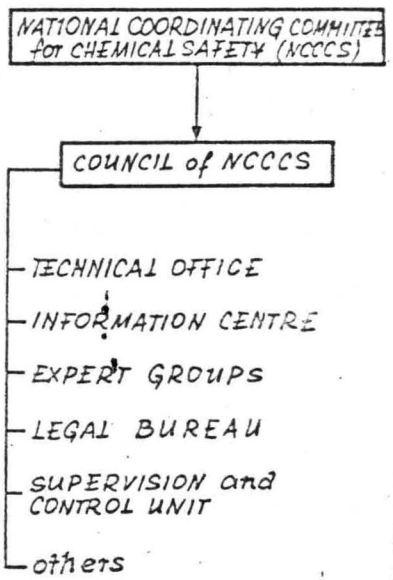


Jean
Prof (Anal).
9/12/87 London

NORM SETTING AND CONTROL

IN

MANAGEMENT OF CHEMICAL RISK

LONDON - NOV. 1987

Reyes, F. G. R

Almeida, W. F.

NORM SETTING AND CONTROL

IN

MANAGEMENT OF CHEMICAL RISK

DEVELOPING COUNTRIES:

1.ST. PHASE - AGRICULTURAL ACTIVITIES

+

A FEW INDUSTRIES

E.G.: SEVERAL AFRICAN COUNTRIES

2ND. PHASE - AGRICULTURAL ACTIVITIES

+

NEW INDUSTRIAL AREAS IN QUICK DEVELOPMENT

E.G.: INDIA, MÉXICO, BRAZIL

(RECENTLY INDUSTRIALIZED COUNTRIES)

INDUSTRIES IN DEVELOPING COUNTRIES

1. BRANCHES OF
   MULTI-NATIONAL COMPANIES

   —— OLD PLANTS
      TRANSFERRED TO DEVING COUNTRIES

   —— LOCAL PERSONS IN CHARGE:
      WITHOUT INFORMATION OF
      CHEMICAL RISK

   —— CHEMICALS - PRODUCED OR IMPORTED:
      . NOT PERMITTED
        IN OTHER COUNTRIES
      . INFERIOR GRADE (IMPURITIES)

2. SMALL NATIVE INDUSTRIES
   WITHOUT ANY INFORMATION ON
   CHEMICAL SAFETY
   TOX. & ECOTOX. PROBLEMS

NORM SETTING IN DEVELOPING COUNTRIES

1ST. CASE: A FEW LAWS -

CONTROL OF SOME WELL KNOWN
DANGEROUS CHEMICALS

E.G.: A LIST OF APPROVED PESTICIDES

ECONOMICAL & TECHNICAL CRITERIA

HEALTH PROBLEMS
&
ENVIRONMENTAL IMPACT
} NOT CONSIDERED

NORM SETTING IN DEVELOPING COUNTRIES

2ND. CASE:

MANY LAWS, DECREES & REGULATIONS

ADOPTED
&
ADAPTED
} FROM INDUSTRIALIZED COUNTRIES

. NO DISCUSSION ON THE REASONS
FOR THE THEORETICAL LIMITS

. NO MONITORING

. NO ENFORCEMENT OF THE LEGISLATION

NON-ENFORCEMENT OF THE LEGISLATION

IN DEVELOPING COUNTRIES

ALLEGED REASONS:

- LACK OF FUNDING
- SHORTAGE OF STAFF
- LACK OF EXPERTISE
- DELAY IN THE PROJECTS
- LACK OF ADMINISTRATIVE COORDINATION

CONSEQUENCES:

- MONITORING ABSENT
- REAL SITUATION NOT KNOWN
- HIGHLY POLLUTED CITIES
- HEALTH IMPAIREMENT OF THE POPULATION

REAL REASONS FOR THE

NON EXISTENCE OR NON ENFORCEMENT

OF THE LEGISLATION

- POPULATION NON-INFORMED OR MIS-INFORMED

- DECISION MAKERS WITHOUT GOOD ADVISERS

- LACK OF ENTHUSIASM

- HIGH PRESSURE BY THE MULTI-NATIONAL INDUSTRIES

- CORRUPTION

HEALTH IMPAIREMENT

ACUTE, SHORT-TERM AND LONG-TERM EFFECTS

MANY TIMES NOT CORRELATED TO THE REAL CAUSES

EXAMPLES:

- INDISCRIMINATE USE OF PESTICIDES.
- VOLATILE ORGANIC COMPOUNDS IN THE ATMOSPHERE.
- INADEQUATE HANDLING, USE AND DISPOSAL OF CHEMICALS.
- WRONG USE OF HAZARDOUS CHEMICALS.
- INDUSTRIAL PLANTS WITH OLD EQUIPMENT RESPONSIBLE FOR ENVIRONMENTAL POLLUTION.
- ANTI-POLLUTION EQUIPMENT NOT INSTALLED FOR ECONOMICAL REASONS.

ACUTE POISONING BY PESTICIDES

CASES	PERIOD	MORBILITY	MORTALITY Nº	MORTALITY %
COMMUNICATED				
- STATE OF SAO PAULO(1)	1967-1979	3481	208	6%
DETECTED				
IN ARAUCARIA(2) (AGRIC. TOWN)	1984-1985	3283	264	8%

(1) ALMEIDA, 1984.

(2) STATE DEPT OF HEALTH, PARANA - BRAZIL.

ACCIDENTS REPORTED TO 10 POISON CONTROL CENTRES IN DIFFERENT AREAS OF BRAZIL

	YEAR			
	1982		1983	
MEDICAL DRUGS	27%		33%	
POISONOUS ANIMALS	21%		11%	
HOUSEHOLD PRODUCTS	12%		11%	
CHEMICALS	10%	30%	10%	29%
PESTICIDES	8%		8%	
TOXIC PLANTS	5%		4%	
OTHERS	17%		23%	
Nº OF REPORTED CASES	6856		14791	

(MIN. HEALTH. BRAZIL, 1984).

PESTICIDE POISONING

IN

COSTA RICA (CENTRAL AMERICA)

YEAR	Nº OF CASES	% OF TOTAL POISONING CASES
1978	307	29.3
1979	423	20.3
1980	593	19.9
1981	491	14.7
1982	613	16.7
1983	790	19.0

(INCER. 1984).

MERCURY IN URINE(X) -

ARGENTINIAN CHILDREN USING

PHENYL-MERCURIC ACETATE TREATED DIAPERS

Hg (µg/liter)	% of Children
Less Than 12	12%
12–20	5%
21-40	11%
41-100	29%
101-200	33%
201–450	10%

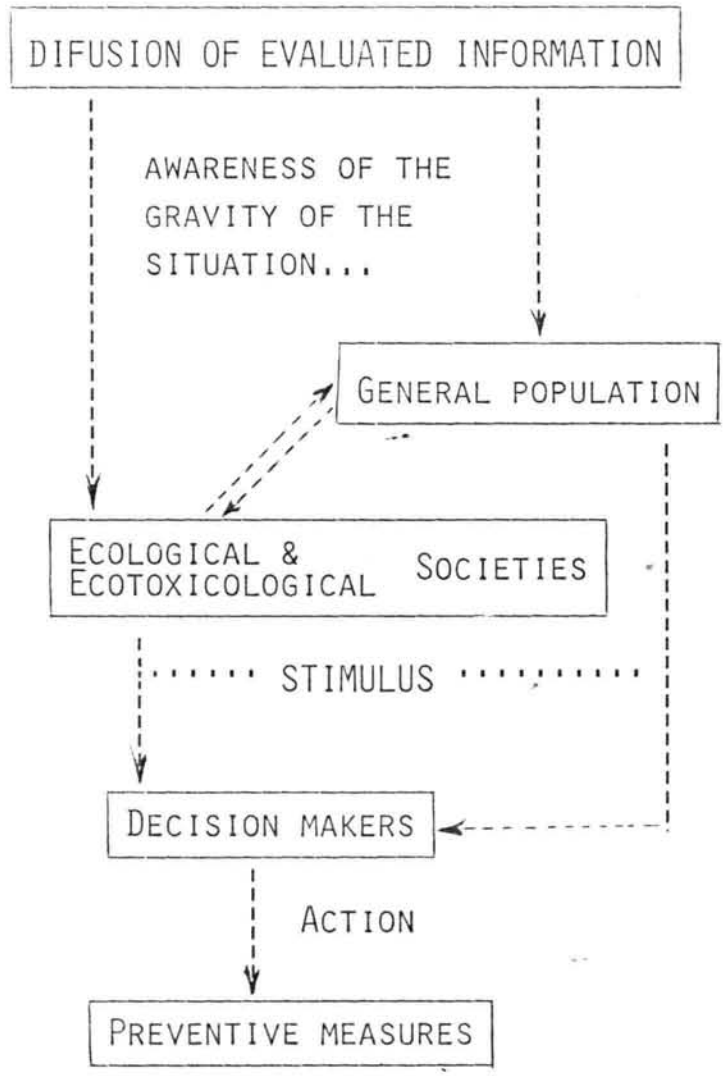
(Croce, 1984)

(x) Data from 301 children

NOTE: 15000 children contaminated with phenyl mercuric acetate used for "sanitation" of diapers.

ACTIONS TO BE TAKEN

1. PREVENTIVE MEASURES



ACTION TO BE TAKEN

2. ACCESS TO EXISTING INFORMATION SOURCES

THROUGH INTERNATIONAL CHANNELS

PUBLICATIONS - WIDE DIFFUSION NEEDED

IPCS/WHO - ENVIRONM. HEALTH CRITERIA SERIES

EURO/WHO - HEALTH ASPECTS OF CHEMICAL SAFETY

ECO/PAHO/WHO - PUBLICATIONS ON ECOTOX. AND CHEMICAL SAFETY

IARC - MONOGRAPHS AND OTHER PUBLICATIONS

UNEP/IRPTC - DATA PROFILES FOR CHEMICALS

UNEP/IRPTC - LEGAL FILE

WHO/UNEP/ILO - SENTINEL

GEMS - PUBLICATIONS ON ECOTOXICOLOGY

ACTIONS TO BE TAKEN

3. MANPOWER DEVELOPMENT

- LABORATORY TRAINING
- INTER-LABORATORY STUDIES
- BILATERAL AGREEMENTS
- COURSES:
  - POST-GRADUATE COURSES
  - SHORT-TERM COURSES
  - SEMINARS & WORKSHOPS

CENTRAL COORDINATION

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
IPCS/WHO/ILO/UNEP

ACTION TO BE TAKEN

4. NETWORK OF SUPPORTING & CO-OPERATING INSTITUTIONS

- PERMANENT EXCHANGE OF INFORMATION
- DEVELOPMENT OF ADEQUATE METHODOLOGIES
- NEW AND MORE EFFECTIVE APPROACHES
- SHORT-TERM ADVISERS
- FELLOWSHIPS - SPECIAL TRAINING
- EXPERT COMMITTIES

CENTRAL CO-ORDINATION - HARMONIZATION

IPCS