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N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)
CAS N°:101-72-4

SIDS Initial Assessment Report
for
SIAM 10

Tokyo, 15-17 March 2000

Chemical Name: N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)

CAS No: 101-72-4

Sponsor Country: United Kingdom

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HISTORY:

The SIDS Dossier and Testing Plan were reviewed at the 3rd SIDS Review Meeting where the following SIDS Testing Plan was agreed:

no testing	()
testing	(x)

Testing on developmental toxicity/teratogenicity was underway at the time of the review meeting.

The SIDS Initial Assessment Report was discussed at SIAM 6 in 1997. It was recommended that the report should be re-drafted and presented to a future SIAM.

COMMENTS:

The SIAR for SIAM 10 has been re-structured to emphasise the hazards in line with the refocused SIDS programme. The principal changes to the text concern human health (mutagenicity and developmental toxicity) end points. The exposure estimates for the environment are now in an annex, which includes some additional data on emissions from tyres although the calculations have not been changed. Any further work required for this substance is a post SIDS activity.

Date of Circulation: 11th February 2000

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-72-4
Chemical Name	N-Isopropyl-N'-phenyl-p-phenylenediamine (IPPD)
Structural Formula	$\text{CH}_3\text{CH}(\text{CH}_3)\text{NH}-\text{C}_6\text{H}_4-\text{NH}-\text{C}_6\text{H}_5$
RECOMMENDATIONS	
The chemical is a candidate for further work.	
SUMMARY CONCLUSIONS OF THE SIAR	
The health and environmental effects database meets the requirements for the SIDS data package .	
Human Health	
<p>In a poorly reported human study, there is some evidence for uptake via the skin and bioaccumulation of IPPD. However, due to the poor quality of the study, no conclusions could be drawn on the extent of absorption. A single briefly reported animal toxicokinetic study indicated that IPPD does not readily penetrate unbroken skin, although no further information is available. IPPD is absorbed from the gastrointestinal tract, although no quantitative information is available on the extent of absorption.</p> <p>There is no information on the effects of IPPD following acute inhalation, oral or dermal exposure in humans. However, IPPD is of moderate toxicity by the oral route in rats (typical $\text{LD}_{50} = 800 \text{ mg/kg}$), and of very low toxicity by the dermal route in rabbits. No information is available regarding acute inhalation toxicity in animals. Evidence from human and animal studies suggests that IPPD is not a skin irritant. Animal studies also suggest that IPPD is not an eye irritant. Animal evidence demonstrates that IPPD is a skin sensitiser, and human evidence from volunteer studies and case-reports is consistent with this. There are no data available on respiratory sensitisation. No information was available concerning repeat exposure of humans to IPPD. No useful animal inhalation or dermal data are available. There were no findings of any toxicological significance in a 90-day oral rat study at three highest dose, 57 mg/kg/day, and this may be regarded as a NOAEL. In a 28-day study a NOAEL of 223 mg/kg/day, the highest dose administered, was identified.</p> <p><i>In vitro</i> mammalian cell mutagenicity assays demonstrate IPPD has a potential to induce chromosome aberrations in the absence or presence of exogenous metabolic activation. The potential for direct acting genotoxicity was also demonstrated in a study of sister chromatid exchange. Negative results have been obtained in a number of <i>in vitro</i> genotoxicity studies (Ames, mammalian cell gene mutation, and unscheduled DNA synthesis). No carcinogenicity data are currently available. There were no fertility studies available, but in a 90-day repeat dose study there was no histological evidence of adverse effects in the reproductive organs of male and female rats exposed at the top dose of 57 mg/kg/day. In the only developmental toxicity study available, skeletal changes consistent with ossification retardation were observed at doses that did not produce maternal toxicity. NOAELs of 125 mg/kg/day and 62.5 mg/kg/day were identified for mothers and offspring, respectively. The relevance of this finding for human health hazard identification is uncertain.</p>	
Environment	
<p>Acute toxicity data are available for four fish species, three showing similar sensitivity. The lowest 96-hour LC_{50} is 0.34 mg/l for Rainbow trout (<i>Oncorhynchus mykiss</i>). A 14-day LC_{50} of 0.09 mg/l was obtained for fathead minnow (<i>Pimephales promelas</i>), which may indicate that IPPD (or its breakdown products) has cumulative toxicity. Aquatic invertebrates appear to be less sensitive, the 48-hour EC_{50} for <i>Daphnia magna</i> being 1.1 mg/l (NOEC of 0.56 mg/l). A 96-hour EC_{50} of 0.4 mg/l is reported for green algae. A PNEC of 0.34 $\mu\text{g/L}$ can be derived for the aquatic</p>	

environment using an assessment factor of 1000 with the acute toxicity result for rainbow trout.

IPPD hydrolyses rapidly (over timescales similar to those of the static tests), so some of the toxic effects may be due to hydrolysis products. One of the fish studies used flow-through conditions, with similar toxicity at 96 hours to that shown in the static tests. It therefore appears that IPPD is of similar toxicity to the hydrolysis products.

Exposure

Around 10,000 -15,000 tonnes of IPPD are produced worldwide each year. It is used as an anti-degradant in rubber, mainly for car tyres. Potential release to the environment can occur from manufacture, the production of rubber for tyres, tyres in use and on disposal. Exposure to humans is expected to occur only via the workplace.

IPPD is a solid of low water solubility (~15 mg/l) and an octanol-water partition coefficient ($\log K_{ow}$) of 3.9. Its atmospheric half-life is estimated to be between 23 and 54 minutes. It hydrolyses in water with half-lives between 2 and 11 hours depending on the water source. Biodegradation studies show rapid primary degradation but low ultimate degradation, indicating that the breakdown products may be persistent. IPPD has a potential to bioaccumulate in aquatic organisms (based on its $\log K_{ow}$). It can be predicted that the substance will remain in water or soil once it reaches there, although degradation is expected to be rapid. Most of the release to air is also rapidly degraded but that which is not is quickly removed to water and soil.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is a candidate for further work post-SIDS as follows:

1. There is some uncertainty about which chemical species produce the toxic effects on aquatic organisms. Whilst the SIDS endpoints are fulfilled, toxic effects are apparent at low concentrations and so further investigation of the nature and properties of breakdown products could be performed.
2. The hazards to the aquatic environment and to human health due to skin sensitisation are such that member states are invited to investigate the relevance of exposure conditions in their country. In this context, further information on the persistence of IPPD in tyres and the quantities leached during the lifetime of the tyre would be useful for an environmental assessment.
3. An *in vivo* bone marrow study (micronucleus) using parenteral administration would be useful to investigate the potential observed *in vitro* for direct acting clastogenicity.

SIDS INITIAL ASSESSMENT REPORT

1 IDENTITY

OECD Name:	N-isopropyl-N'-phenyl-p-phenylenediamine (IPPD)
CAS Registry Number:	101-72-4
IUPAC Name:	1,4-benzenediamine, N-(1-methylethyl)-N'-phenyl
Molecular Formula:	C ₁₅ H ₁₈ N ₂
Molecular weight:	226.32
Degree of Purity:	97%
Major Impurity:	main impurities contain a second isopropyl group (on either nitrogen) or do not contain the isopropyl group
Essential Additives:	None

Physico-chemical properties

Very few data are available in the literature on the physico-chemical properties of this substance. The values quoted below are usually those obtained from manufacturers and have not been independently validated. The exact methods used to measure some of the parameters are not known.

Physical state

The substance exists as dark purple to black flakes depending on manufacture and purity. It has been reported to have an aromatic odour (Monsanto, 1992) but the odour threshold is not known.

Melting point

The melting range has been quoted as approximately 73-75°C (Monsanto, 1992) and as 78°C (Kirk-Othmer, 1992). Bayer quote it as > 75°C. The Monsanto value is thought to have been established using a capillary tube method (Monsanto Analytical Method E08-001). The British Rubber Manufacturers Association (1990) quotes a melting point of 73°C. These values are consistent with variation in manufacture and purity.

Boiling point

The boiling point has been quoted at 220°C at 1.33 kPa (Bayer AG) and at 161°C at 0.133 kPa (Monsanto).

Density

The density (specific gravity) has been quoted as 1.01-1.07 at 25°C (Monsanto, MSDS).

Vapour pressure

The vapour pressure has been quoted as 0.000093 kPa at 50°C (Spract et al, 1964) and 0.00046 kPa at 90°C (Monsanto, 1992) and 0.21 kPa at 180°C and 1.3 kPa at 213°C (Bayer AG, MSDS).

Water solubility

The solubility in water has been measured at approximately 15 mg/l and the substance can therefore be considered practically insoluble (Monsanto study). It is understood that the method used was extraction with dichloromethane (100% recovery at 1 ppm) with analysis by gas chromatography (2 m Ultrabond column, 210°C).

Octanol-water Partition coefficient (K_{ow})

A log K_{ow} value of 4 has been calculated (Leo, 1989) whilst a value of 3.88 is quoted by a manufacturer (Monsanto, 1992).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production

IPPD is made by the reductive alkylation of 4-nitrodiphenylamine with acetone. The annual production volume is estimated to be 10,000-15,000 tonnes worldwide.

2.2 Use pattern

The substance is used as an anti-degradant in rubber, its mode of action involving reaction at the rubber surface with atmospheric compounds to form a protective film of complex products. It is added to rubber formulations at levels of 1-2%. The rubber is shaped and moulded and then vulcanized to produce the finished article. This results in the inclusion of IPPD into the rubber matrix. The main use is in the production of tyres. It can be used in open and closed systems.

2.3 Environmental exposure

Potential release to the environment can occur at four stages of the life cycle: manufacture of IPPD; production of rubber articles containing IPPD; losses from articles in use; and losses on disposal. Release may occur to water and to air, or it may go to solid waste. An environmental exposure estimate for the aquatic compartment for different stages of the life cycle is provided in Annex 3, for information.

2.4 Human exposure

Occupational exposure

No occupational exposure data are currently available.

Consumer exposure

IPPD is well known as a severe allergen and its use is usually avoided in non-industrial applications (Feinman, 1987). Therefore most reactions to IPPD or related compounds have been from occupational causes (Cronin, 1980). Reactions have formerly been seen to shoes, sports equipment and tyres. IPPD found in Bulgarian underwear in the 1960s was documented to be responsible for allergic reactions and in Iran shoes made from tyres produced a similar response (Leppard and Parhizgar, 1977). A squash ball has also been described as a culprit in a series of tests between 1965 and 1976 (Cronin, 1980). More recently a case of allergy from grasping rubber from a windsurf wishbone (Tennstedt and Lachapelle, 1981) and from the rubber round a diving mask (Maibach, 1975) were described.

However owing to the known propensity of IPPD to cause a severe allergic response it is thought unlikely that it is used in any current consumer products.

Indirect exposure via the environment

As discussed below, abiotic processes rapidly degrade IPPD. Hence significant exposure to humans through the environment is not expected to occur.

3 ENVIRONMENT EFFECTS

3.1 Fate & Distribution

Atmospheric degradation

No information on degradation in air is available in the SIDS. The Syracuse Research Corporation program AOP was used to estimate the reaction rate in air with hydroxyl radicals; this gave a half-life of 23 minutes. This calculation involved the use of an assumed rate for one of the contributing reactions; even if this were neglected the half-life would still be only 54 minutes. A printout from the program is included in Annex 1.

Aquatic degradation

Abiotic degradation

No information is available on aqueous photolysis. A number of studies have shown that IPPD is hydrolysed in water with a half-life of less than one day. For example, primary degradation in deionised water was measured in a study that showed 68% degradation after 25 hours (Monsanto 1978c).

A further study showed the effect of varying the quality of the water. Using a river die-away test the chemical transformation half-lives in purified water, membrane-filtered river water and unfiltered river water were 11, 5 and 2 hours respectively (Monsanto 1981a).

A third study on hydrolysis in deionised water at pH 7, 25°C found that 99% of the IPPD had hydrolysed after 24 hours. The major product was benzoquinoneimine-N-phenyl, with 4-hydroxydiphenylamine as a minor product. Isopropylamine was also detected (Monsanto 1992).

Biodegradation studies

Limited biodegradation studies indicate that the hydrolysis products may be more persistent than the parent substance. In one test using activated sludge (method similar to EPA method in US EPA 40 GFR Ch 1, subpart D, paragraph 796.3100), carbon dioxide evolution was 18.9% of the theoretical value after 32 days. The authors state that considering the rapid primary degradation of IPPD the failure to obtain significant CO₂ evolution suggests the formation of more persistent metabolites or degradation products (Monsanto 1978c). In another test in which oxygen consumption was monitored no evidence for biodegradation was observed.

Accumulation and metabolism

A bioconcentration factor of 170 can be calculated based on a log octanol-water partition coefficient of 3.9, indicating a potential to accumulate in aquatic organisms.

Environmental distribution

The distribution of IPPD was modelled using the FUGMOD model as distributed by the OECD using the generic parameters. Most of the physico-chemical data required are available. However the vapour pressure was measured at an elevated temperature. The ChemEst program was used to estimate the value at 25°C from structure, giving a value of 2.1×10^{-3} Pa.

Measured degradation data are only available for hydrolysis in water. Also available is a predicted value for the degradation rate in air; the longer half-life as described above was used in the calculations (subsequent use of the shorter half-life made very little difference to the results). Both of these processes were included in the first model runs; a nominal release rate of 1000 kg/hour was used for each of air, water and soil in turn. A release of 750:250 kg/hour water:soil was also used.

The results are given in Annex 2. They show that IPPD released to water tends to partition to sediment to some extent due to the high log K_{ow} but that the residence time in this case is short (4 hours). Releases to soil remain there to a large degree, so removal depends on transfer back to air or to water and is slow. The majority of the release to air is removed by degradation; rain-out removes some of the rest to water, where it reacts rapidly, and more to soil where it tends to persist. With a mixed release the main removal process is degradation in water, with some degradation in air; the chemical tends to build up in soil and the residence time is increased to 634 hours. In all the release scenarios there is very little removal from the region by flow.

As IPPD hydrolyses in water it seems likely that this will also occur in the water in the two 'solid' phases of the model, soil and sediment. There is no information on this in the SIDS, although a modelling exercise supplied by industry used a half-life of 10 hours in both compartments. In the current assessment values of 10x the half-life in water, i.e. 20 hours, were used; this is an arbitrary choice. The results are also in Annex 2. The effect of including these removal processes is to decrease the proportion of IPPD found in the soil when the release is to air. The sediment is now less important in terms of the proportion of chemical it contains from releases to water. Overall the residence times decrease, now all being around 2 hours with the exception of release only to soil where it is nearly 30 hours.

The overall pattern is that the chemical tends to remain in water or soil once it reaches there, whether directly or via the air. Hydrolysis in water is rapid, and whilst it may persist longer in soil it seems likely that hydrolysis will occur here too (although there is no direct evidence for this). Most of the release to air is rapidly degraded there but that which is not is quickly removed to water and soil.

These calculations and comments refer to the parent compound. They do not consider the potential fate of breakdown products from the reaction of IPPD in water.

3.2 Toxicity test results

The overall information contained in the SIDS dossier is sufficient for initial environmental hazard identification and classification purposes.

Fish

Acute toxicity data for IPPD are summarised in Table 1. 96-hour LC_{50} s for three species of fish range from 0.34 to 0.43 mg/l.

A further acute study was reported in the IUCLID Data Sheet. From a static test on *Brachydanio rerio* a 96-hour LC_{50} of 12.5 mg/l was obtained. Analytical monitoring was carried out. It is not clear why this result differs from the others.

Table 1: Toxicity of IPPD to fish

Species	Parameter	Concentration, mg/l	NOEC, mg/l	Reference
Bluegill sunfish <i>Lepomis macrochirus</i>	96-h LC ₅₀	0.43 (0.35-0.51)	Not stated	Monsanto (1977)
Rainbow trout <i>Oncorhynchus mykiss</i>	96-h LC ₅₀	0.34 (0.26-0.44)	Not stated	Monsanto (1977)
Fathead minnow* <i>Pimephales promelas</i>	96-h LC ₅₀	0.41 (0.36-0.46)	Not stated	Monsanto (1979)

* Flow-through study

The results are based on nominal concentrations and static test conditions (EPA guidelines).

Monsanto (1979) carried out a dynamic 14-day toxicity study with fathead minnow (*Pimephales promelas*) using a flow-through proportional diluter. This is considered to be an extended acute study. A 14-day LC₅₀, based on measured concentrations, was calculated to be 0.09 (0.078-0.10) mg/l. The authors state that using acute toxicity curves generated from both nominal and measured water concentrations the lethal threshold had not been reached within the 14-day test. The results indicated that IPPD appeared to have cumulative toxicity.

Aquatic invertebrates

Acute toxicity data for IPPD to the water flea *Daphnia magna* are summarised in Table 2.

Table 2: Toxicity of IPPD to daphnids

Organism	Parameter	Concentration, mg/l	NOEC, mg/l	Reference
<i>Daphnia magna</i>	48h-LC ₅₀	1.1 (0.85-1.5)	0.56	Monsanto (1978d)

The results are based on nominal concentrations and static test conditions (EPA guidelines).

Toxicity to algae

Acute toxicity data for IPPD are summarised in Table 3.

Table 3: Toxicity of IPPD to algae

Species	Parameter	Endpoint	Concentration, mg/l	Reference
Green alga	96-h EC ₅₀	<i>In vivo</i> chlorophyll <i>a</i>	0.4 (0.1-2.0)	Monsanto (1978e)
<i>Selenastrum capricornutum</i>	96-h EC ₅₀	cell number	0.5 (0.2-2.0)	Monsanto (1978e)

The results are based on nominal concentrations and EPA guidelines.

Other organisms

Acute toxicity data for IPPD to other aquatic organisms are summarised in Table 4.

Table 4: Toxicity of IPPD to other organisms

Species	Parameter	Concentration, mg/l	NOEC, mg/l	Reference
midge larva <i>Paratanytarsus parthenogenetica</i>	48-h LC ₅₀	23 (21-26)	*	Monsanto 1981b

* - a no effect level was not observed since the lowest level (10 mg/l) caused 15% mortality after 48 hours.

The results are based on nominal concentrations and static test conditions (EPA guidelines).

There is no information on toxicity to soil dwelling organisms for the hydrolysis products of IPPD, although this is not expected to be a principle exposure route.

Comments on aquatic toxicity tests

The rapid hydrolysis of IPPD must be considered when reviewing the available aquatic test results. The half-life for this has been measured in waters of various degrees of purity with values from 2 to 16 hours. Even at the slowest rate, six half-lives will have elapsed in a 96-hour test; this would leave less than 2% of the original concentration. This may imply that most of the effects seen in static tests are due to the hydrolysis products. In most of the studies the IPPD concentration was not monitored and so there is no information on this from the actual tests. The one static study that did include analytical monitoring gave a much higher value than the other fish toxicity tests, at 12.5 mg/l. It is not clear why this result is different from the others.

The static tests with rainbow trout and bluegill show progressive toxicity, the value of the LC₅₀ decreasing with increasing exposure time. This suggests that the effects seen are not due simply to an initial exposure to the parent compound.

There is one longer-term study, over 14 days, which used flow through conditions. In this case it may be assumed that the organisms were exposed to IPPD rather than the breakdown products. Concentrations of IPPD were monitored in this study, and remained close to the nominal levels throughout. It is interesting that the 96-hour LC₅₀ determined in this test is very similar to those obtained through static tests, which suggests that IPPD and its hydrolysis products may have similar acute toxicities. The final 14-day LC₅₀ value is lower, indicating that IPPD may have cumulative effects. A no-effect concentration was not established in this test.

4 HUMAN HEALTH

4.1 Toxicokinetics, metabolism and distribution

Animals and humans

In a poorly reported animal study, the tails of an unstated number of mice were 3/4 immersed in 50% oil of IPPD for an unstated length of time (Stasenkova, 1970). It was stated that IPPD did not readily penetrate unbroken skin although no further information is available.

In a poorly reported human study, urine was collected twice daily (pre- and post-shift) over a 2 week period from 16 people occupationally exposed to IPPD during the curing of rubber (Scansetti et al, 1987). No information was provided as to the route, level or duration of exposure. The weekly mean levels of IPPD in the urine were reported to increase from 19.55 to 83.57 µg/l for pre- to post-shift respectively. During the working week there was also some evidence of accumulation of IPPD in the body with the pre-shift urine levels increasing from 10.8 to 25.8 µg/l for Monday to Friday respectively. However, the quality of the information is such that few conclusions can be drawn.

In the same report, in order to evaluate the potential for dermal absorption the study author immersed one hand in 10 litres of cold water containing 2 g of undissolved IPPD for 90 minutes and collected urine samples at unstated intervals over 7 days. IPPD was detected in the urine 3 hours after the end of exposure and ceased to be detected in the urine 7 days after exposure. This study provides evidence of dermal absorption of IPPD. However, due to the poor quality of the study, no conclusions can be drawn on the extent of absorption.

Acute and repeated dose oral studies indicate that IPPD is absorbed following this route of exposure, although no quantitative information is available on the extent of absorption.

4.2 Acute toxicity

Studies in animals

Inhalation

No reports were available.

Oral

Rats

In a study, only available as an abstract, 0/5, 2/5, 4/5 and 5/5 deaths occurred in rats administered 631, 794, 1000 or 1260 mg/kg IPPD respectively by gavage (Monsanto, 1974). Muscular weakness and reduced appetite were also reported although no information was given on dose levels at which these effects were seen. At autopsy, 14 days after administration, lung hyperaemia, slight liver discolouration and gastro-intestinal inflammation were apparently observed although as above no information was provided on the number of animals affected or the dose at which these effects were seen. An oral LD₅₀ of 900 mg/kg was obtained from this study.

In a brief report, an LD₅₀ of 800 mg/kg was stated to have been determined in rats (Stasenkova, 1970). The chemical was stated to have a "marked narcotic action" although no further information was provided.

Similar rat oral LD₅₀ values have been documented in a number of other studies (Hecht and Kimmerle, 1963; de Gubareff, 1958; Marhold, 1972 and Bourne et al, 1968) which were not obtained.

Mice

In two briefly reported studies, LD₅₀ values for IPPD in mice of 3030 and 3592 mg/kg were determined (Stasenkova, 1970; Vorob'eva, 1963). No further information was available.

Mouse oral LD₅₀ values of 2250 and 2300 have apparently been documented (Rhone-Poulenc, 1972; Rhone-Poulenc, 1973) although these reports were not obtained. Another mouse study which was not obtained apparently reported an oral LD₅₀ value of 1122 mg/kg (Mel'nokova et al, 1967).

Dermal

In a study, only available as an abstract, no deaths occurred following dermal administration of 5010 or 7940 mg/kg IPPD as a 40% solution in corn oil to 1 and 2 rabbits respectively (Monsanto, 1974). At autopsy, 14 days after administration of the chemical, the viscera were reported to be normal. No further information is available.

IUCLID cites an old unpublished study and a secondary literature source in which LD₅₀ and LD_{L0} values of >7500 mg/kg were obtained in rabbits (de Gubareff, 1958; McCormick, date unstated).

Studies in humans

No information is available on single dose toxicity of IPPD in humans by either the inhalation, oral or dermal routes.

Summary of single exposure studies

There is no information on the effects of IPPD following acute inhalation, oral or dermal exposure in humans. IPPD is of moderate toxicity by the oral route in rats, and of very low toxicity by the dermal route in rabbits. No information is available regarding acute inhalation toxicity in animals.

4.3 Irritation

Studies in animals

Skin

In a study, only available as an abstract, 500 mg of IPPD was applied as a fine powder to the pre-moistened skin of 6 rabbits for 24 hours (Monsanto, 1974). The animals were maintained for 7 days and the scores for erythema and oedema recorded at 4, 24, 48, 72 and 168 hours after removal of the dressing. The scores were zero at all timepoints for all animals indicating that IPPD is not a skin irritant in this study.

In a briefly reported study, 500 mg of vaseline containing 2.5% or 25% IPPD was applied to the scarified and unscarified skin of groups of 6 rabbits (Herve-Bazin, 1977). The animals were examined for erythema and oedema at 24 and 72 hours, although the erythema was stated to be difficult to read due to skin colouration. The severity of the irritation was described as limited and moderate at 2.5% and 25% respectively, although from the limited data provided it is unclear if these levels of reaction were in the scarified or unscarified skin.

Two other unpublished dermal irritation studies are listed in IUCLID which apparently indicate that IPPD is either slightly or not irritating to rabbit skin (Hecht and Kimmerle, 1963; de Gubareff, 1958)

Eye

In a study, only available as an abstract, 100 mg of finely ground IPPD was applied to one eye of 6 rabbits for 24 hours (Monsanto, 1974). The grading system used is not clearly stated in the abstract, however the conjunctival erythema observed at 24 hours in all the animals was described as being only "slight". There was no evidence of eye irritation at 48 hours in any of the animals.

Two other old studies are listed in IUCLID which apparently indicate that IPPD is either not or only slightly irritating to the eye (Hecht and Kimmerle, 1963; de Gubareff, 1958). One reference cited in IUCLID suggests that 100 mg IPPD applied to the eye of an unstated number of rabbits for 24 hours produced moderate irritation although no further details are available (Marhold, 1986).

Studies in humans

Two old unpublished studies in humans, available as brief abstracts indicate that IPPD is either slightly or not irritating to human skin (Hecht and Kimmerle, 1963; Shelanski, 1961). However, the brief nature of the reporting in these studies is such that no conclusions can be drawn. There is no information on eye irritation in humans.

Summary of irritation

Evidence from human and animal studies suggests that IPPD is not a skin irritant. Animal studies also suggest that IPPD is not an eye irritant.

4.4 Corrosivity

The skin and eye irritation studies in animals and humans indicate that IPPD is not corrosive.

4.5 Sensitisation

Studies in animals

In a maximisation test, groups of 20 guinea pigs were induced using an unstated number of intradermal injections of 0.5% IPPD followed 1 week later by a topical application of 1% IPPD (Herve-Bazin et al, 1977). The animals were challenged 1 week after the topical induction, at a naive site with either 0.5% or 0.05% IPPD in vaseline. Skin sensitisation reactions were recorded in 70% of the animals challenged with 0.5% IPPD and in 10% of those challenged with 0.05% IPPD. None of the control animals challenged with either 0.05% or 0.5% showed a skin response.

In a well reported mouse local lymph node assay which is considered to be acceptable as a positive screen for OECD purposes, 0, 0.1, 0.5, 1 or 2% IPPD was administered to both ears of groups of 3 mice on 3 consecutive days (Ikarasghi et al, 1993). The mice were sacrificed on the fourth day at which time the auricular lymph nodes were excised and the cells cultured with ^3H -methyl thymidine ($^3\text{HTdR}$). Lymph node cell proliferation was measured by scintillation counting of $^3\text{HTdR}$ incorporation. A positive result was considered by the author to be a cell proliferation score of 2 times greater than controls. This was calculated to have occurred at an IPPD concentration of 0.14% suggesting that IPPD be considered a strong sensitiser. Current methodology suggests a score 3 times greater than controls as being positive. From the dose-response curve it was calculated that a concentration of less than 0.5% would have given a response 3 times greater than the controls. Overall this study indicates that IPPD should be considered a strong sensitiser.

In a briefly reported, poor quality study, 50% IPPD was applied as a paste daily to the skin of an unstated number of guinea pigs for 20 days (Stasenkova, 1970). No information is given on the use of controls. It was stated that no marked skin irritation was observed during induction. After 20 applications, a naive site was challenged with 10-100% IPPD. Apparently a 'positive result' was obtained with 100% IPPD although no further details were provided.

Studies in humans

In a paper by Alfonzo (1979) it is noted that IPPD is routinely included (as part of a PPD mix) in standard patch testing series for contact dermatitis in a London hospital specialising in skin diseases. A PPD-black rubber mix is included in the European Standard Contact Dermatitis Testing Battery, although the components of this PPD-mix are not clearly defined and IPPD is not specifically listed.

In a poor quality human volunteer study hampered by confused reporting, IPPD or another similar chemical was tested for skin sensitising potential over a 6 week period in a large number of volunteers, although the exact number involved in the IPPD test is not clear (Monsanto, 1978a). During the induction stage, 0.2 ml of 1% IPPD in petrolatum was applied dermally at the same site for 48-72 hours three times a week for three weeks. Approximately fourteen days after the last induction period the volunteers were challenged for 48-72 hours at a naive site with 1% IPPD. Reactions to the challenge were scored at 96 hours after application of IPPD. It was stated that 12 out of 82 volunteers (approximately 15%) dermally exposed to IPPD became sensitised. There was apparently a high unexplained drop out rate which cannot be accurately quantified from the raw data and it is not clear whether 82 represents the total number of volunteers in the IPPD test.

In a brief case report of a tyre worker with dermatitis of the hands and chest, a positive response was obtained in a patch test with IPPD (Ancona et al, 1982). The worker wore no personal protective equipment at work, and as part of his duties came into daily direct contact with rubber tyres many of which were identified as containing an unstated amount of IPPD. However, co-exposure to rubber, solvents and mechanical trauma also occurred in this occupation, and therefore the exact cause of the occupational dermatitis is unclear.

A number of other papers have reported patients who show a positive reaction when patch tested with IPPD (Roed-Petersen et al, 1977; Herve-Bazin et al, 1977; Alfonzo, 1979; Tuyp and Mitchell, 1983). Some of these patients were potentially occupationally exposed to IPPD in rubber during the production of tyres and in wearing rubber fingerstalls. In another patient, exposure to a rubber mask used in scuba diving with thought to have caused IPPD sensitisation. However, due to co-exposure to other chemicals, and cross-reactivity with other chemicals, it is unclear if IPPD is responsible for the sensitisation.

Summary of sensitisation

Animal evidence demonstrates that IPPD is a skin sensitiser. Human evidence from volunteer studies and case-reports is consistent with this. There are no data available on respiratory sensitisation.

4.6 Repeated dose toxicity

Studies in animals

Inhalation

In a briefly reported study, an unstated number of rats were exposed by inhalation to 300-400 mg/m³ aerosolised IPPD for 2 hours/day for 15 days (Vorob'eva, 1963). However from the few details available it is not possible to draw any firm conclusions from this study concerning the health effects associated with repeat inhalation exposure.

Oral

In a well conducted 28 day study, groups of 10 rats (5 per sex) were exposed to 0, 500, 1000, 1750 or 2500 ppm IPPD daily in the diet (equivalent to approximately 46, 93, 155 and 223 mg/kg/day) (Biodynamics, 1988a). No deaths occurred during the study at any dose level. Although body weight gain in males at 1750 and 2500 ppm was 30% less than controls at the end of the dosing period, this is associated with a 30% decrease in food consumption noted in these groups at week 1 and is therefore not of toxicological significance. Increases in total protein of up to 17% above control values were noted in males at all doses and in females at 1000 ppm and above. In males a statistically significant increase in platelet counts were noted from 1750 ppm and statistically significant decreases in haematocrit were noted from 1000 ppm. Male and female relative liver weight was increased by 72% and 44% respectively over controls at 2500 ppm. Relative adrenal and spleen weight was increased in males at 2500 ppm by 20% and 32% respectively. There were no treatment-related gross pathological or microscopic changes observed at any dose level and the clinical chemistry, haematological and organ weight changes were not considered to be of toxicological significance. A NOAEL of 2500 ppm (approximately 223 mg/kg/day) is determined.

In a well conducted 3 month study, groups of 20 rats (10 per sex) were exposed to 0, 180, 360 or 720 ppm IPPD in the diet (equivalent to approximately 15, 29 and 57 mg/kg/day) (Biodynamics, 1988b). Physical, clinical chemistry and haematological examinations were conducted at regular intervals throughout the study. No deaths occurred and there were no treatment related effects on bodyweight or food consumption noted during the study. No toxicologically significant haematological and clinical changes were observed. In high-dose males and females relative liver weight was increased over controls by 41% and 52% respectively and absolute liver weight by 35% and 48% respectively. High-dose females also showed an increase in relative kidney and spleen weight of 20% and 26% respectively. However, these organ weight changes were not associated with gross or microscopic pathology changes and are therefore of doubtful toxicological significance. A NOAEL of 720 ppm (approximately 57 mg/kg/day) is determined.

Two brief, poor quality reports were obtained in which IPPD was administered by gavage to either rats for 24 days or rabbits for 4 months (Stasenkova, 1970; Vorob'eva, 1963). However, the quality of the reporting is such that no useful information can be obtained from these studies concerning the health effects associated with repeat oral exposure.

A mouse study was reported in IUCLID in which an unstated number of animals were orally dosed by gavage with up to 1000 mg/kg/day IPPD for 8 days (Hazleton, 1983). A total of 7/10 animals were reported to have died in the high dose group, but no clinical signs of toxicity were apparently observed in any dose group.

Dermal

No data are available.

Studies in humans

No inhalation, dermal or oral data are available

Summary of repeat dose toxicity

No information was available concerning repeat exposure of humans to IPPD. No useful animal inhalation or dermal data are available. There were no findings of any toxicological significance in a modern well-conducted 90-day oral rat study, and therefore a NOAEL of 720 ppm (57 mg/kg/day), the highest dose administered, was identified. In a 28 day study a NOAEL of 2500 ppm (223 mg/kg/day), the highest dose administered, was identified.

4.7 Mutagenicity

In vitro studies

Bacterial studies

In a well-conducted Ames plate incorporation assay, IPPD did not produce an increase in revertants in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1538 in the presence or absence of Aroclor-induced rat liver S9 (Monsanto, 1986a). IPPD was tested up to cytotoxic concentrations. The positive controls gave appropriate responses.

In a well reported plate incorporation Ames study, IPPD did not produce an increase in revertants in *Salmonella typhimurium* strains TA 98 or TA 100 in the presence or absence of Aroclor-induced rat liver S9 (Crebelli et al, 1984). The chemical was stated to have been tested up to the highest non-toxic dose. The positive control gave an appropriate response.

There are a number of other published Ames studies conducted with IPPD which also apparently gave negative results (NTP, 1984; Donner, 1983; Rannug, 1984; Vasilyeva, 1985; Yamaguchi, 1991) which were not obtained.

Mammalian cell studies

The ability of IPPD to induce chromosome aberrations and sister chromatid exchange has been investigated in Chinese Hamster ovary (CHO) cells for the US NTP (NTP unpublished data, 1990 from the Central Data Management at NIEHS, USA) apparently using the method described by Galloway et al (1985; 1987). Only a brief summary of the raw data is available.

CHO cells were exposed to 1.6, 3, 5 and 10 micrograms/ml in the absence of exogenous metabolic activation and harvested at 13 h. The nature of the aberrations was not fully described. However, it was reported that gaps and endoreduplications were excluded from the data presented and the

remaining effects were categorised as “complex” (exchanges and rearrangements), “simple” (breaks and terminal deletions), “other” (includes pulverized chromosomes) and “total”. In the first experiment severe toxicity was observed at the top dose. A dose-related increase in the frequencies of total and simple aberrations were reported, however, no clear dose-response was apparent in complex aberrations and the overall result of this experiment was regarded as equivocal and the experiment was repeated. In the second experiment, dose levels of 3, 5, 7.5 and 10 micrograms/ml were used and the harvest time was reported to be 17.5 h. No cytotoxicity was reported. Large, statistically-significant and dose-related increases in the frequencies of total, complex and simple aberrations were observed. No information is available on the exact nature of the aberrations, however, it would be prudent regard this result as positive.

A single experiment was performed in the presence of rat liver derived S9 using IPPD concentrations of 10, 16, 30 and 50 micrograms/ml. Severe toxicity was observed at the top dose level. Compared to concurrent solvent controls, clear increases in the frequencies of total, complex and simple aberrations were observed at all dose levels tested and these results met the performing laboratory's criteria for a positive result (2 doses producing statistically significant increases).

The ability of IPPD to induce sister chromatid exchange in CHO cells was also investigated. In the absence of exogenous metabolic activation cells were exposed for 26 h to 0.05, 0.16, 0.5, 1.6 and 5 micrograms IPPD/ml. Fifty cells per dose were scored. In the first experiment severe toxicity was observed at the top dose tested. Compared to the concurrent solvent control, a small statistically significant increase (31%) in SCE was observed at the next dose level tested, 1.6 micrograms/ml. These results did not meet the performing laboratory's criteria for a positive result i.e. 2 doses producing SCEs 20% greater than control. In the repeat of the experiment, no cytotoxicity was reported. A marked concentration-related induction of SCEs was observed with values of 22%, 36%, 89% and 134% at 1, 1.6, 3 and 5 micrograms/ml respectively. In the presence of rat liver S9, no dose-response relationship was apparent following a 2 h treatment with IPPD (0.5 - 16 micrograms/ml) whilst cells exposed at a concentration of 50 micrograms/ml were cytostatic. Positive control substances demonstrated that the system was capable of detecting SCE.

Negative results were obtained in a well conducted hprt gene mutation assay using Chinese Hamster Ovary cells (Monsanto, 1986b). The cells were treated with 3, 10 or 30 µg/ml IPPD in the presence or absence of Aroclor-induced rat liver S9 activation. Reductions in colony counts of 84% and 95% with and without activation respectively were observed at the top dose. A negative and positive control group were included and produced acceptable results.

Negative results were obtained in a tk gene mutation assay using mouse lymphoma L5178Y cells (Monsanto, 1978b). The cells were treated with 0.0195 to 10 µg/ml IPPD, in the presence or absence of Aroclor-induced rat liver S9 activation. Relative growth of the cells was reduced to 10% at 2.5 µg/ml without activation and to 25% at 10 µg/ml with activation. No significant or dose-related increases in the frequency of mutant cells were seen in the main test. A second independent confirmatory experiment was not conducted. A negative and positive control group were included and produced acceptable results.

Negative results were also obtained in a well conducted *in vitro* unscheduled DNA synthesis assay, rat hepatocyte cultures were treated with 0.01 to 10 mg/ml IPPD (Monsanto, 1986c). Cytotoxicity (described as unscorable slides) was observed with concentrations of 3 mg/ml and above. A negative and positive control group were included and produced acceptable results.

In vivo studies

No data are currently available.

Studies in humans

There is no information available.

Summary of mutagenicity

In vitro mammalian cell mutagenicity assays demonstrate IPPD has a potential to induce chromosome aberrations in the absence or presence of exogenous metabolic activation. The potential for direct acting genotoxicity was also demonstrated in a study of sister chromatid exchange. Negative results were obtained in vitro with respect to gene mutation and unscheduled DNA synthesis. No in vivo data are available.

4.8 Carcinogenicity

No data are currently available.

4.9 Toxicity for Reproduction**Studies in animals***Effects on fertility*

No fertility studies were available. However in a 90-day oral study there were no significant histopathological changes in either the testes, epididymides, ovaries or accessory sex organs of rats treated with up to 57 mg/kg/day IPPD.

Developmental studies

In a developmental toxicity study, groups of 24 female rats were administered 0, 12.5, 62.5 or 125 mg/kg/day IPPD by gavage on days 6-15 of gestation (Safepharm, 1993). The females were killed on day 20 of gestation at which time the uterine contents were examined. No maternal deaths occurred and there were no treatment-related effects on bodyweight at any dose level although food consumption was significantly reduced in high dose animals on the first 3 days of dosing. Soft stools and pre-dosing salivation was also reported in high dose animals. The apparent lack of maternal toxicity indicates that the study was not sufficiently rigorous. There were no differences in the number of corpora lutea per dam or the ratio of dead / live foetuses per litter in any treatment group. Uterine and implantation data as well as foetal external and visceral findings indicated no treatment related effects at any dose level. In the high dose group an increase was observed in the number of foetuses with ossification variations including irregularly and incompletely ossified cranial and facial bones, no ossification of the hyoid, semi-bipartite vertebral centra and unilateral / bilateral wavy ribs. However, these skeletal changes are considered indicative of ossification retardation and provide insufficient evidence for considering IPPD as a developmental toxicant. NOAELs of 125 mg/kg/day and 62.5 mg/kg/day were identified for the mothers and offspring respectively.

In a screening study, 800 mg/kg IPPD was administered by oral gavage to a group of 50 pregnant mice on gestation days 6 to 13. Due to the severe mortality observed (48/50 animals) no useful information on reprotoxic parameters can be drawn from this study (Chernoff and Kavlock, 1982; 1983).

Summary of Reproductive toxicity

There were no fertility studies available, but in a 90-day repeat dose study there was no histological evidence of adverse effects in the reproductive organs of male and female rats. In the only developmental toxicity study available, skeletal changes consistent with ossification retardation were observed at doses that did not produce maternal toxicity. Due to the lack of maternal toxicity at the highest dose tested, it is unclear whether more severe developmental effects would occur at higher dose levels.

4.10 Summary of Effects on Human Health

The only information available on the potential human health effects of IPPD comes from studies and case reports in workers and consumers repeatedly dermally exposed to rubber products that contain IPPD.

In a poorly reported human study, there is some evidence for uptake and bioaccumulation of IPPD. However, due to the poor quality of the study, no conclusions could be drawn on the extent of absorption. A single briefly reported animal toxicokinetic study indicated that IPPD does not readily penetrate unbroken skin, although no further information is available. Information from acute and repeated dose oral studies indicate that IPPD is absorbed following this route of exposure, although no quantitative information is available on the extent of absorption.

There is no information on the effects of IPPD following acute inhalation, oral or dermal exposure in humans. However, IPPD is of moderate toxicity by the oral route in rats (typical LD₅₀ = 800 mg/kg), and of very low toxicity by the dermal route in rabbits. No information is available regarding acute inhalation toxicity in animals. Evidence from human and animal studies suggests that IPPD is not a skin irritant. Animal studies also suggest that IPPD is not an eye irritant. Animal evidence demonstrates that IPPD is a skin sensitiser, and human evidence from volunteer studies and case-reports is consistent with this. There are no data available on respiratory sensitisation. No information was available concerning repeat exposure of humans to IPPD. No useful animal inhalation or dermal data are available. There were no findings of any toxicological significance in a modern well-conducted 90-day oral rat study, and therefore a NOAEL of 720 ppm (57 mg/kg/day), the highest dose administered, was identified. In a 28-day study a NOAEL of 2500 ppm (223 mg/kg/day), the highest dose administered, was identified.

In vitro mammalian cell mutagenicity assays demonstrate IPPD has a potential to induce chromosome aberrations in the absence or presence of exogenous metabolic activation. The potential for direct acting genotoxicity was also demonstrated in a study of sister chromatid exchange. Negative results have been obtained in a number of *in vitro* genotoxicity studies (Ames, mammalian cell gene mutation, and unscheduled DNA synthesis). No carcinogenicity data are currently available. There were no fertility studies available, but in a 90-day repeat dose study there was no histological evidence of adverse effects in the reproductive organs of male and female rats. In the only developmental toxicity study available, skeletal changes consistent with ossification retardation were observed at doses that did not produce maternal toxicity. Due to the lack of maternal toxicity at the highest dose tested, it is unclear whether more severe developmental effects would occur at higher dose levels.

Risks to human health*Workers*

As no occupational exposure data are available it is not possible to carry out an adequate risk assessment for occupational risk assessment. Further information would be needed to assess this risk.

Consumers

There have been a number of cases of skin sensitisation reported in the literature that have been thought due to IPPD. However, as IPPD is known to cause such a severe allergic response it is not thought to be in use in any current consumer products and therefore poses no risk to consumer health.

Man exposed indirectly via the environment

Although no exposure information is available, IPPD does not persist in the environment and so it is considered unlikely to present a risk through indirect exposure.

5 CONCLUSIONS AND RECOMMENDATIONS

The chemical is a candidate for further work as follows:

- 1) The rapid hydrolysis of IPPD in water means there is some uncertainty about which chemical species produce the toxic effects. It is clear that the substance does not remain in the parent form for long in water, and hence it is assumed that the toxic effects seen in the static tests are due at least in part to hydrolysis products. As toxic effects are seen at low levels of IPPD further research could be initiated to determine the identity of these hydrolysis products (and their effects) as a post SIDS activity. Information could also be gathered on the biodegradation of the hydrolysis products (from the information available it appears that they are not readily biodegradable).
- 2) As IPPD is very toxic to aquatic organisms, relatively small releases to water could lead to risks. Better information about potential releases from IPPD production and rubber production could be collected locally to identify if there are any significant releases (in particular information on how much can actually get into water and how much is solid waste). For releases from tyres, it would be useful to have more information on the persistence of IPPD in the rubber, quantities leached from rubber (or abraded rubber) during the lifetime of the tyre and the form of the substance if released. These are post-SIDS requirements.
- 3) Information on worker exposure may be recommended in order to assess the risks in the workplace. In light of the declining use of the substance the UK consider a national occupational exposure survey to be of low priority and no further work is currently anticipated in this area.
- 4) An in vivo bone marrow study (micronucleus) using parenteral administration would be useful to investigate the potential observed in vitro for direct acting clastogenicity.

6 REFERENCES

Bayer AG , MSDS (date n/k)

Biodynamics Inc, BD-88-74 (1988a) A 4 week range finding toxicity study with Santoflex IP in the rat via dietary admixture.

Biodynamics Inc, BD-88-389 (1988b) A sub-chronic (3 month) oral toxicity study with Santoflex IP in the rat via dietary admixture.

Bourne, H.G et al. (1968). Arch. Environ. Health. 16: 700-705.

British Rubber Manufacturers Association Guide to Toxicity and safe handling of Rubber Chemicals (code of practice, 1990 Edition)

Chernoff, N. and Kavlock, R.J. (1982). An in vivo teratology screen utilizing pregnant mice. J. Toxicol. Environ. Health., 10, 541-550.

Chernoff, N. and Kavlock, R.J. (1983). A teratology test system which utilizes postnatal growth and viability in the mouse. In: Waters et al (1983). Short term bioassays in the analyses of complex environmental mixtures; Vol III, Plenum Publishing Company, pp 417-427.

Crebelli, R., Falconi, E., Aquilina, G. and Carere, A. (1984). In vitro mutagenicity of rubber chemicals and their nitrosation products. Toxicology letters 23: 307-313.

Cronin E. (1980) In Contact Dermatitis Cronin E (Ed). Churchill Livingstone. Edinburgh pp714-770.

de Gubareff, Monsanto data, short report, July 9, 1958.

Donner, M. et al. (1983). Scand J. Work Environ. Health 9 Suppl 2: 27-37.

Feinman S. E. (1987) Sensitivity to rubber chemicals. J. Toxicol. - Cut & Ocular Toxicol 6(2), 117-153.

Galloway S., et al (1987). Chromosome aberration and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Molec. Mutagen., 10 (suppl. 10), 1-176.

Galloway S., et al (1985). Development of a standard protocol for in vitro genetic testing with Chinese hamster ovary cells: Comparison for 22 compounds in 2 laboratories. Environ Mutagen, 7, 1-51.

Hazleton Study nos. 6125-101 through 6125-110, Screening of priority chemicals for potential reproductive hazard, NTIS PB85-220143, December 6, 1983.

Hecht and Kimmerle (1958). Bayer AG data, short report. October, 1958.

Herve-Bazin, B., Gradski, D., Duprat, P., Marignac, B., Fousereau, J., Cavelier, C. and Bieber, P. (1977). Occupational eczema from N-isopropyl-N'-

phenylparaphenylenediamine (IPPD) and N-dimethyl-1,3 butyl-N'-phenylparaphenylenediamine (DMPPD) in tyres. Contact Dermatitis 3: 1-15.

Ikarashi, Y., Tsuchiya, T. and Nakamura, A. (1993). Evaluation of contact sensitivity of rubber chemicals using the murine local lymph node assay. Contact Dermatitis 28: 77-80.

INFU (1997). Exemplarische Erfassung der Umweltexposition ausgewählter Kautschukderivate bei der bestimmungsgemäßen Verwendung in Reifen und deren Entsorgung. Institut für Umweltforschung Universität Dortmund, July 1997.

Jolly, A. M., Willoughby, B., Karras, G. C. and Hobbs, S. J. (1994). Use Category Document: Plastics Additives. BRE

Kirk-Othmer, Encyclopaedia of Chemical Technology, 5th Edition, Volume 2, 1992

Leo, A.: CLOGP-3.54 MEDChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA.

Leppard B. J. & Parhizgar B. (1977) Contact dermatitis to PPD rubber in Maleki shoes. Contact Dermatitis 3, 91-93.

Maibach H. I. (1975) Scuba diver facial dermatitis: Allergic contact dermatitis to N-isopropyl N'-phenylparaphenylenediamine. Contact Dermatitis 1,330.

Marhold, J.V. (1972). Sbornik Vysledku Toxixologickeho Vysetreni Latek A Pripravku. p72

Marhold, J.V. (1986). Prehled Prumyslove Toxicol. Org Latky 483.

McCormick, W.E., Rubber Chemistry and Technology, p633.

Mel'nikova, L.V., Mater. Nauch.-Prakt. Konf. Molodykh Gig. Sanit. Vrachei, 11th 185-187 (1967), cited in Chem. Abstr. 72: 41136d (1970).

Monsanto Study No: ES-78-SS-20

Monsanto, Y-73-287 (1974). Acute oral study in rats, Acute dermal study in rabbits, Dermal irritation study in rabbits, Eye irritation study in rabbits.

Monsanto (1977) Acute (96-hour) toxicity of Santoflex IP to rainbow trout and bluegill. Unpublished report

Monsanto study, MA-78-93 (1978a) Modified draize skin sensitisation study.

Monsanto study, BO-78-224 (1978b) Mutagenicity evaluation of Santoflex IP in the mouse lymphoma forward mutation assay.

Monsanto (1978c) Environmental persistence screening of selected rubber chemicals. Unpublished report

Monsanto (1978d) Acute toxicity of Santoflex IP to the water flea (*Daphnia magna*). Unpublished report

Monsanto (1978e) Acute toxicity of Santoflex IP to the green alga (*Selenastrum capricornutum*). Unpublished report

Monsanto (1979) Dynamic toxicity of Santoflex IP to fathead minnows (*Pimephales promelas*). Unpublished report

Monsanto Internal Report (August, 1980)

Monsanto (1981a) Environmental fate screening (river die-away study) of Santoflex IP. Unpublished report

Monsanto (1981b) Acute toxicity of Santoflex IP to midge (*Paratasytarsus parthenogenetica*). Unpublished report

Monsanto study, ML-85-243 (1986a) Ames/Salmonella mutagenicity assay of Santoflex IP.

Monsanto study, ML-85-221 (1986b) CHO/HGPRT Gene mutation assay with Santoflex IP.

Monsanto study, SR-85-251 (1986c) Evaluation of the potential of Santoflex IP to induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

Monsanto, MSDS (1992)

Monsanto (1993) Unpublished report. Cited in OECD SIDS dossier for IPPD.

National Toxicology Programme Annual Plan for fiscal year (1984), February 1984

National Toxicology Programme Annual Plan for fiscal year (1988).

National Toxicology Programme Unpublished data (1990)

Rannug, A. et al. (1984). Prog Clin Biol Res. 141: 407-419.

Rhone-Poulenc data, unpublished results, Note D.S. 49850- du 11/12/72.

Rhone-Poulenc data, unpublished results, Note D.S. 51.365- July 9, 1973.

Roed-Petersen, J., Hjorth, N., Jordan, W.P. and Bourlas, M. (1977). Postsorters' rubber fingerstall dermatitis. Contact Dermatitis 3: 143-147.

Safepharm 543/2 (1993) IPPD: Oral gavage teratology study in the rat.

Saito, H., Katsumi, M. and Arita, T. (1980). Biological fate of phenylisopropyl-p-phenylenediamine. Yakugaku Zasshi 100 (2): 126-132.

Scansetti, G., Buglione, E., Massiccio, M. M., Gregghi, D., Inglese, L., Pisani, W. and Pavan, I. (1987). Excretion kinetics of the rubber anti-oxidant N-isopropyl-N'-phenyl-p-phenylenediamine (IPPD).

Shelanski, M.V. (1961). Monsanto data, short report, November 13.

Spract, R.B. et al., Rubber Chemistry and Technology, 211-220 (1964)

Stasenkova, K.P. (1970). Toxic properties of certain stabilisers for vulcanisates. *Soviet Rubber Technology*. 29: 25-26.

Tennstedt D. & Lachapelle J. M. (1981) Windsurfer dermatitis from black rubber components. *Contact Dermatitis* 7, 160-161.

Tuyp, E. and Mitchell, J.C. (1983). Scuba diver facial dermatitis. *Contact Dermatitis* 3: 334-5.

Vasilyeva, L. et al. (1985) *Gig. Trud. Prof. Zabol.* 8: 16-19.

Vorob'eva, R.S., Zhilova, N.A., Kasparov, A.A. and Mezentseva N.V. (1963). Comparative toxicity of mercaptobenzimidazole and N-phenyl-N-isopropylparaphenyleneamine. *Soviet Rubber Technology*. 22: 11-12.

Yamaguchi, T. et al (1991). *Eisei Kagaku* 37(1): 6-13.

Annex 1: Copy of output from AOP model

SMILES : CC(C)Nc1ccc(cc1)Nc2ccccc2
CHEM : IPPD
MOL FOR : C15 H18 N2
MOL WT : 226.32

----- SUMMARY: HYDROXYL RADICALS -----

Hydrogen abstraction = 18.6715 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 120.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec
**Addition to Aromatic Rings = 200.0000 E-12 cm3/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant = 338.6715 E-12 cm3/molecule-sec
HALF-LIFE = 0.032 days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 22.748 min

.....** Designates Estimation (s) using ASSUMED Values

----- SUMMARY: OZONE REACTION -----

***** NO OZONE REACTION ESTIMATION *****
(ONLY Olefins and Acetylenes are Estimated)

Annex 2: Results of Distribution Modelling

Model used: FUGMOD - Fugacity Level III program as prepared for OECD Workshop, Version 1, Jan 1992. Generic settings.

Data used:

Property	Value (source)
Molecular weight	226.32 (SIDS)
Water solubility	15 mg/l (SIDS)
Log octanol-water partition coefficient	3.88 (SIDS)
Vapour pressure	2.1x10 ⁻³ Pa (ChemEst estimate)
	1x10 ⁻⁵ Pa (estimate from SRC Henry calculation)*
Half life in water	2 hours (SIDS)
Half life in air	0.9 hours (estimate from SRC AOP program)
Half life in soil*	20 hours (chosen as 10x water half life)
Half life in sediment*	20 hours (chosen as 10x water half life)

Values marked * were only used in some of the calculations (see main text).

Results

1. Data used - higher vapour pressure, no degradation in soil or water

Phase	Release (kg/h)	Amount (%)	Degraded (%)	Advected (%)	Residence time (h)
Air	1000	0.1	97.7	1.3	2524
Water			1.0		
Soil		99.9			
Sediment					
Air					4
Water	1000	71.7	99.7	0.3	
Soil		0.6			
Sediment		27.7			
Air			14.3	0.2	248818
Water			85.3	0.3	
Soil	1000	100			
Sediment					
Air	250	0.1	24.4	0.3	634
Water	750	0.3	75.0	0.2	
Soil		99.5			
Sediment		0.1			

2. Data used - higher vapour pressure, degradation in soil and water

Phase	Release (kg/h)	Amount (%)	Degraded (%)	Advected (%)	Residence time (h)
Air	1000	81.0	97.6	1.3	1.6
Water		0.3	0.2		
Soil		18.7	1.0		
Sediment					
Air					2.9
Water	1000	99.9	99.7	0.3	
Soil					
Sediment		0.1			
Air					28.9
Water					
Soil	1000		100		
Sediment					
Air	500	28.5	48.8	0.6	2.2
Water	500	64.9	49.9	0.1	
Soil		6.6	0.5		
Sediment		0.1			

Annex 3: Environmental exposure estimates

A quantified assessment is only possible for the aquatic environment, and this requires the use of modelled concentrations as no measured levels are available.

Potential releases

The areas for consideration are production, use in rubber production, use of rubber products and disposal.

RELEASE FROM PRODUCTION

There is no information in the SIDS about releases from the production of IPPD. One manufacturer suggested that releases of the substance to water from production were <0.1%, and that IPPD was not detected in the effluent; however no detection limit was given.

In order to address this stage the EU Technical Guidance for risk assessment of new and existing substances has been used. Annual world production of IPPD is 10,000-15,000 tonnes. Assuming half of this is made in Europe, then 2,500 tonnes is taken as the capacity of a manufacturing site. If production operates for 300 days then the daily production rate is 8.3 tonnes. From the Technical Guidance release tables, the releases are:

to air - 0.001%
to water - 0.3%

These give 83 g/day released to air and 24.9 kg/day released to water.

Release from rubber production

Information on releases from rubber production is taken from a Use Category Document (UCD) on Plastics Additives (Jolly et al 1994) produced in the UK.

IPPD is likely to be used in a similar way to anti-oxidant chemicals in plastics production. Its vapour pressure at 150-200°C places it into the group considered to have high volatility in the report. Tyre forming is assumed to be a closed process involving the use of moulds.

Three areas of release are dealt with in the UCD:

- i) Raw materials handling, from their arrival on site to their addition to polymers. There may be retention in the containers used to transport the chemical (25 kg sacks for IPPD from the SIDS), losses as dust when removing from the containers and adding to the polymer. Losses here are considered to be related to the particle size of the material; as there is no indication in the SIDS of the size of IPPD particles used, then the worst case assumption of a fine (<40 µm) powder will be made. It will be assumed that material remaining in the containers is dealt with as solid waste. The UCD estimates the worst-case release from emptying containers to be 0.5%, with a further 0.1% from wear and tear on the containers during handling. These releases will initially be to air but the dust will eventually settle and may then be swept up and disposed of as solid waste. Wet cleaning operations will result in any residual materials being released to water.

It is not possible to apportion the release between these two routes; as a worst case it could be assumed that all of the 0.6% released goes to waste water.

- ii) Compounding, where the additives are mixed with the polymer. Losses here can occur as dust or by volatilisation. These are expected to be much lower than those in handling and are estimated as 0.06% in total. Again, these losses are likely to be split between solid waste and water, and again the worst case assumption of all to water will be made. IPPD is added to rubber in tyre production at a level of 1-2%.
- iii) Conversion of the compounded material into the rubber article, in this case tyres. As this is a closed process losses are considered to be minimal; the UCD suggests a value of 0.01%. Again this will be assumed to go to water.

These figures give a possible overall release factor to water of 0.67% from tyre production.

In the absence of any specific information on the scale of tyre production it will be assumed that 1000 tonnes of IPPD is used on one site in the production of 50,000 to 100,000 tonnes of rubber. For 300 days of operation this gives a daily use rate of 3.3 tonnes; at a release of 0.67% this gives 22 kg/day to water.

The solid waste releases are assumed to be treated as chemical waste and disposed of accordingly.

Release from tyres in use

Comments on the fate of IPPD in rubber tyres in use were provided by industry in an Annex to the SIDS as follows:

The prime role of IPPD in tyres is to protect the exterior surfaces from oxygen, sunlight and ozone. The mechanism suggested for this function is the formation of a flexible film through reaction with ozone; this film is then resistant to further attack. Friction between the road surface and the wearing surface of the tyre - i.e. essentially the tread - will abrade this film. Migration of IPPD from the bulk of the tyre to the surface results in regeneration of the film. Any IPPD in a free form that is lost would be contained in the rubber dust particles that are removed by the abrasion. It would be expected to be rapidly oxidised in this state. Contact with water would also result in hydrolysis.

This appears to be a realistic assessment of the behaviour of IPPD. Kirk-Othmer (1992) comments that in addition to scavenging ozone, p-phenylenediamines also react with it to produce high molecular weight products which act as a physical barrier to ozone attack. As the surface film is removed by abrasion then the layer immediately below that is brought to the surface will presumably contain IPPD so that it may not be necessary to assume large-scale migration of the chemical. The function of the chemical is to react with species from the air and calculations indicate that this should be rapid. It therefore seems unlikely that IPPD will exist as a free chemical in the environment for long. There is also the likelihood of hydrolysis if free chemical were to come into contact with water, although the products of this may be of similar toxicity. Taken as a whole the evidence suggests that IPPD itself will not reach the environment in significant quantity through its

use in tyres. It is more likely that it will be in the form of reaction products (currently unidentified).

INFU (1997) carried out a series of experiments on leaching of additives from rubber in tyres. They found that IPPD could be leached from samples of abraded rubber (particles) from both old and new tyres, using distilled water and artificial acid rain (pH 4). The acid rain tended to produce higher solution concentrations in the short-term extractions. IPPD was also found in water from longer term experiments in which larger rubber samples were partly immersed in water or acid rain. Here there was little difference between the concentrations at pH 7 and pH 4. Analyses were carried out at 2-month intervals that may indicate that under some conditions IPPD is more stable in water. Samples of rainwater runoff from motorways were also analysed; IPPD was not detected in these samples (detection limit 8 µg/l).

As an indication of the amount of tyre wear which might be found, a rate of 188 mg/km/vehicle can be estimated, as sedimentary and direct transfer to road surface particulates (Handbook of Emission Factors 1980). In the UK, a realistic high average daily traffic flow is 78,000 vehicles/km/day (for motorways) (Office of National Statistics 1996). This would give a daily release of 14.7 kg of rubber per kilometre. Assuming a level of 2% in rubber, the maximum amount of IPPD released per kilometre would be 0.29 kg/day. This takes no account of any degradation of IPPD in the abraded rubber, and also assumes that all abraded rubber deposited on the road contains IPPD at a level of 2%. Other anti-degradants are in use so this is an over-estimate of the release of IPPD.

An estimate of the proportion of tyres containing IPPD is as follows:

Method 1:

15,000 tonnes of IPPD are used. At 2% in rubber, this gives 7.5×10^5 tonnes of rubber.

Taking 12 kg as average tyre weight, this corresponds to 6.25×10^7 tyres.

Assume that IPPD is used across Western Europe and North America. Total number of tyres produced in this area is 4.36×10^8 per year. So the proportion containing IPPD is 14%

Method 2:

Assume that use is evenly distributed across Western Europe and North America. Also assume that the fraction used in each country is proportional to the vehicle distance travelled in that country.

Total traffic distance in Western Europe and North America is 6.1×10^{12} km.

Total traffic distance in UK is 4.4×10^{11} km (7%).

So estimate that 7% of tyres contain IPPD.

The proportion of tyres containing IPPD is therefore probably in the range of 7-14%.

Release from disposal

No information is available on whether tyres at the end of their lifetime still contain IPPD. If tyres are incinerated then IPPD is expected to be destroyed. If the rubber is reused then there may be release of remaining IPPD, or there may need to be further addition of the chemical to provide the anti-degradant function. No information is available on this area, but it might be considered that the assessment of the original manufacture of the tyres would cover this area.

Predicted Environmental Concentrations (aquatic compartment)

Production

It is assumed that the aqueous release of 24.9 kg/day goes to a sewage treatment plant (STP) with a capacity of 2000 m³/day, giving a concentration in the inflow of 12.45 mg/l. IPPD is not readily biodegradable. The tables of removal percentages based on physico-chemical properties in the Technical Guidance give a distribution of 44% to sludge and 56% to water for a non-degradable chemical with IPPD's properties. This gives a concentration in the effluent of 7 mg/l. Assuming a default dilution factor of 10 gives the concentration in the receiving waters as 0.7 mg/l.

This calculation does not take into account the effect of hydrolysis. IPPD hydrolyses quite rapidly in water, with a half life of 2 hours in unfiltered river water which is the closest medium tested to that in the waste disposal system. This means that the chemical will be decomposing as it moves down in the discharge from the production site to the STP, in the STP itself and in the river after the treatment plant. The model of the STP used to estimate removal assumes a hydraulic residence time of 10 hours; as this is five times the half-life in river water then 97% hydrolysis would be expected. This would reduce the concentration in the effluent to 0.21 mg/l and the concentration in the receiving waters to 21 µg/l. This does not account for any degradation occurring in the time taken to travel from the production site to the STP.

A release to water of <0.1% has been suggested for one site. Assuming a release of 0.1% to water and using other specific information relating to this site (such as the size of the STP, river flow) a concentration of 0.1 µg/l is obtained, without taking hydrolysis into account.

Rubber Production

It is assumed that the release of 22 kg/day to water goes to a sewage treatment plant with a capacity of 2000 m³/day, giving a concentration in the inflow of 11 mg/l. Assuming 44% goes to sludge and 56% to water, the outflow concentration is 6.2 mg/l and the receiving water concentration after a dilution of 10 is 0.62 mg/l. Again this calculation does not take account of hydrolysis. Similar arguments to those above give an outflow concentration of 0.19 mg/l and a concentration in the receiving water of 19 µg/l. Again this does not account for any degradation taking place during the movement from release site to the STW.

Use in Tyres

Assuming all tyres contain IPPD at a level of 2%, the release to the road surface is 0.29 kg/kilometre/day (assuming a width of 15 m, a typical motorway has a surface area per km of $1.5 \times 10^4 \text{ m}^2$). Average rainfall in the EU is 700 mm/year (1.9 mm/day), and the volume of rain for 1 km/day is 28.5 m^3 . Hence the concentration of IPPD in runoff is $0.29/28.5 = 0.01 \text{ kg/m}^3$ or 10 mg/l.

Water flow in standard river from EU guidance is $20,000 \text{ m}^3/\text{day}$, so the concentration in surface water is 14 $\mu\text{g/l}$. Applying a correction for the proportion of tyres actually likely to contain IPPD (7-14%) gives a surface water concentration of 1-2 $\mu\text{g/l}$.

Note that this calculation is based on a number of worst-case assumptions for release to water from tyre wear. For example, it does not take account of degradation (either photodegradation or hydrolysis) and assumes that all the IPPD in abraded rubber is extracted by rainwater. Information on the persistence and availability of IPPD in tyres in use would allow this calculation to be refined.

Other compartments

Concentrations in other compartments have not been calculated. Releases to air from production are estimated to be low, and the reactivity of IPPD in air will result in rapid removal. There may be disposal of IPPD to land from rubber production; this should be as controlled waste. The octanol-water partition coefficient indicates that adsorption to sludge should occur, although the majority of the chemical would be hydrolysed. It is assumed that hydrolysis would continue in the sludge so that any spread on land would not contain significant levels of IPPD. IPPD released from tyres or present in particles abraded from tyres could be washed to soil at the edges of roads. In addition, particles of abraded rubber could be deposited in sediments in water bodies and release IPPD or breakdown products over time. This has not been taken into account in the above assessment.

Implications

Acute toxicity data are available for fish, daphnia and algae. The lowest LC_{50} is 0.34 mg/l, for rainbow trout. From the OECD Assessment Guidance a factor of 100 should be applied to the lowest of at least three acute toxicity results, giving a MTC of 3.4 $\mu\text{g/l}$. From the EU Technical Guidance a factor of 1000 should be used, giving a PNEC of 0.34 $\mu\text{g/l}$.

For production, default values suggest surface water concentrations of 0.7 mg/l without hydrolysis and 21 $\mu\text{g/l}$ with hydrolysis. Both of these give PEC:MTC and PEC:PNEC ratios above 1, giving rise to concern for the aquatic environment. Based on specific data, the surface water concentration from an actual manufacturing site is estimated to be 0.1 $\mu\text{g/l}$ without hydrolysis, which is lower than both the MTC and PNEC values. There is therefore no concern for the aquatic environment for this particular site, and this suggests that the generic exposure estimates should be refined.

For rubber production, surface water concentrations are estimated to be 0.62 mg/l when hydrolysis is not taken into account and 19 $\mu\text{g/l}$ when hydrolysis is included. Both of these give PEC:MTC and PEC:PNEC ratios >1 . There is thus the possibility of effects on the aquatic environment.

A worst-case estimate of possible concentrations arising from release from tyres gave concentrations of 1-2 µg/l in surface water. These are higher than the PNEC but lower than the MTC and suggest the possibility of effects on watercourses receiving run-off from road surfaces. The concentration estimates do not take account of hydrolysis and assume that all the IPPD in rubber abraded from tyres is released. Further data could be gathered to refine this issue.