JACC No 15

1-Fluoro 1,1-Dichloroethane
HFA-141B
CAS No. 1717-00-6

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Joint Assessment of Commodity Chemicals

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1-FLUORO 1,1-DICHLOROETHANE (HFA-141B)

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JACC Report

THE ECETOC SCHEME FOR THE

"JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for reviewing critically the toxicity and environmental hazards of selected industrial chemicals. A number of organisations world-wide produce such reviews so that, based on up-to-date knowledge, existing chemicals can continue to be produced and used safely. ECETOC is contributing to this with its JACC reviews.

In general, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed. Every effort is made to discover whether an adequate review exists already, but when this is not so a review is produced jointly by experts from a number of companies with interests in the chemical. Whenever good scientific reviews on certain toxicological or ecotoxicological aspects exist, their conclusions are summarised and only the subsequent literature is assessed. Only the uses of the chemical as such are considered; its occurrence as an impurity in other products is not normally taken into account.

In this document a critical assessment of the toxicology and ecotoxicology of 1-fluoro 1,1-dichloroethane is presented. Strictly this is not a commodity chemical, it is a product undergoing process development, but in view of the interest that exists in chlorinated fluorocarbons it was considered that an interim statement was needed on the state of knowledge that exists with respect to this group of chemicals.

CONTENTS

1. SUMMARY AND CONCLUSIONS

1-Fluoro 1,1-Dichloroethane (Dichlorofluoroethane) has been proposed as a substitute for fully halogenated chlorofluorcarbons with comparable physical properties since it has more favourable environmental properties.

It is a volatile non flammable colourless liquid, with a weak ethereal odour and moderately soluble in water. The low octanol/water partition coefficient indicates a low potential for bioaccumulation. The physical properties and results of ecotoxicology studies indicate that dichlorofluoroethane presents a low risk to the aquatic environment.

Assuming a 7 year tropospheric lifetime a low ozone depletion potential (ODP) range is 0.065 - 0.14 is expected compared with fully halogenated chlorofluorocarbons such as trichlorofluoromethane (CFC11) and dichlorodifluoromethane (CFC12) with ODP's of 1.0. The global warming potential (GWP) is estimated to be in the range of 0.087 - 0.097, which is low compared to CFC11 (GWP=1.0).

Specific metabolism studies in animals suggest that absorption can occur but no indication was given that metabolism occurs. Although 1% dechlorination of dichlorofluoroethane was observed in vitro studies on rat hepatic microsomes it is probable that if metabolism does occur then it is at a fairly low level.

Dichlorofluoroethane has a low order of acute toxicity. No mortality was observed in rats receiving oral doses of 5000 mg/kg; only piloerection was noted. Dermal exposure of rats or rabbits to 2000 mg/kg also caused no mortality and no signs of toxicity.

Single exposure inhalation studies in mice indicate that the LC_{50} (30 min) was between 300,000 and 500,000 mg/m^3 and the LC_{50} (4h) in rats was 300,700 mg/m^3. Six hours exposure caused narcosis in mice at 198,850 mg/m^3 and pre-narcotic signs were seen in mice and rats at levels higher than 145,500 mg/m^3.

No significant respiratory effects were seen in rats exposed to 45,800 mg/m^3 dichlorofluoroethane for 25 min but at this concentration cardiac sensitisation to adrenaline could be induced in dogs and monkeys. In rats exposed 6h/d for 9 days pre-narcotic signs and increased levels of some plasma components were seen with 41,225 mg/m^3 and above, and a decreased body weight gain in males with 97,000 mg/m^3. A 3-month inhalation toxicity study in rats reported reduced alertness at 97,000 mg/m^3 and slightly increased plasma levels of cholesterol, triglyceride and glucose. No haematological or histopatological changes were observed. The no effect level is considered to be 38,400 mg/m^3.

Liquid dichlorofluoroethane was not an irritant or a sensitising agent to skin, but may cause mild eye irritation.

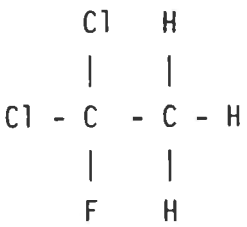
There was no evidence of teratogenic or embryotoxic effects in pregnant rabbits exposed to 6,720, 20,370 or 61,110 mg/m^3 or in pregnant rats exposed to 15,520 or 38,800 mg/m^3 of dichlorofluoroethane. Prenarcotic signs were observed with 15,520 mg/m^3 in rats and 20,370 mg/m^3 in rabbits. A two generation study in rats is planned; and a combined chronic inhalation toxicity/carcinogenicity study in rats with exposure levels up to 97,000 mg/m^3 is in progress.

Dichlorofluoroethane did not demonstrate a significant mutagenic activity *in vitro* or *in vivo*.

2. Identity, Physical and Chemical Properties, Analytical Methods.

2.1 Identity

Chemical structure :



Chemical formula : CCl_2F-CH_3

Common name : 1,1-Dichloro-1-Fluoroethane
Dichlorofluoroethane

Common synonyms : 1-Fluoro 1,1-Dichloroethane
Ethane 1,1-Dichloro-1-Fluoro

HFA-141b*: HCFC 141b: Propellant 141b: R141b

Cas Registry Number : 1717-00-6

Conversion factors : 1ppm = 4.85 mg/m^3
1mg/l= 206 ppm

*HFA-141b abbreviation means : Hydro-Fluor-Alkane : $C_2H_3Cl_2F$

First figure = Number of C-Atoms minus 1	1
Second figure = Number of H-Atoms plus 1	4
Third figure = Number of F-Atoms	1
b represents the isomer	141b

The number of Cl-Atoms is not included in the abbreviations but represents the rest to the total saturation of the formula.

2.2 Physical and Chemical Properties

Dichlorofluoroethane is a non flammable, volatile, colourless liquid at room temperature and normal atmospheric pressure, with a faint ethereal odour. It is moderately soluble in water. Some physical and chemical properties are given in Table 1.

2.3 Analytical Methods

Methods for dichlorofluoroethane analysis described by Coombs et al (1988) are based on gas chromatography with flame ionisation detection and gas chromatography/mass spectrometry.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

There is no known natural source of dichlorofluoroethane. The manufacturing process is still in development and there is no information on production levels; there are no known releases.

Dichlorofluoroethane is being developed as a substitute for existing fully halogenated chlorofluorocarbons with comparable physical properties. These chemicals find applications as blowing agents, solvents, propellants, etc.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Introduction

No information is available on the biodegradation of dichlorofluoroethane in the environment. The low octanol/water partition coefficient (POW <3; see Table 1) makes bioaccumulation of dichlorofluoroethane unlikely.

4.2 Environmental Factors

The physical and chemical properties of dichlorofluoroethane suggest that it would mix rapidly within the lower region of the troposphere by normal conditions. Reaction with naturally occurring hydroxyl radicals (OH) is expected to be the primary degradation route in the troposphere. The tropospheric lifetime related to this reaction is about 7 years (UNEP/WMO, 1989).

The ozone depletion potential (ODP) of dichlorofluoroethane has been estimated to be between 0.066 and 0.092 (one dimensional model) and between 0.065 and 0.14 (two-dimensional model). This is compared to an ODP of 1.0 for the fully halogenated trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC12). The estimates were made assuming the reference gas methyl chloroform has an inferred lifetime of 6.3 years. The stratospheric lifetime of dichlorofluoroethane is shorter than trichlorofluoromethane and slightly longer than methyl chloroform (UNEP/WMO 1989).

The global warming potential (GWP) range for dichlorofluoroethane is in the range of by 0.087 to 0.097 when compared with CFC11 which has a GWP of 1.0 (UNEP/WMO 1989). The range was determined by one dimensional models assuming scaling of HCFC GWPs by methyl chloroform-derived lifetime (6.3 years).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

At the present time, environmental levels and human exposure are negligible, since commercial production of dichlorofluoroethane is just starting.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Data are limited. Environmental testing of dichlorofluoroethane have only been carried out on aquatic organisms.

6.1 Fish Toxicity

The 96 hour - LC_{50} for zebra fish (Brachidanio rerio) was 126 mg/l in a static test using a sealed vessel (Bazzon and Hervouet, 1989).

6.2 Invertebrate aquatic species toxicity

With Daphnia magna, the 48 hour - EC_{50} was 31.2 mg/l using a sealed vessel (Briand and Hervouet, 1989).

From these experiments it can be assumed that dichlorofluoroethane has a low acute toxicity to aquatic organisms.

7. KINETICS AND METABOLISM

7.1 Animal Studies

Some dechlorination (about 1%) was observed (Van Dyke, 1977) when rat hepatic microsomes were incubated with dichlorofluoroethane in vitro.

In a screening test for absorption and metabolism of dichlorofluoroethane (Zwart, 1989), 7 groups of 5 male Sprague-Dawley (Crl:CDBR) rats were exposed to dichlorofluoroethane by inhalation in a closed loop exposure system to fixed initial concentrations ranging from 340 to 12,320 mg/m^3. The exposure durations ranged from 16 to 20 hours. Expired CO_2 was absorbed with soda-lime. The concentration of dichlorofluoroethane in the chamber was continuously monitored by an infra-red analyser. The sensistivity of this technique is such that it will not detect metabolism

of the material below 0.15%. The results suggest that absorption took place but that if any metabolism occurred it was limited. This is in agreement with the results of a sub-acute/sub-chronic toxicity study in which no increase of urinary fluoride was observed in Fischer 344 rats exposed to dichlorofluoroethane at concentrations up to 97,000 mg/m^3 during periods of 4 to 13 weeks (see chapter 8.2).

7.2 Human

No data exist for absorption, distribution, metabolic transformation or elimination of dichlorofluoroethane in man.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO SYSTEM

8.1 Single Exposures

No mortality was observed in rats receiving acute oral doses of 5,000 mg/kg dichlorofluoroethane (Sarver, 1988; Liggett et al, 1988) or dermal doses of 2,000 mg/kg in rats (Janssen and Pot, 1988; Gardner, 1989) and rabbits (Brock, 1988a). Other than piloerection with oral dosing (Liggett et al, 1989) no signs of toxicity were seen. Acute inhalation studies in mice demonstrated a 30 minutes LC_{50} of 485,000 mg/m^3 (Davies et al, 1976). The 4 hour LC_{50} in rats was 300,700 mg/m^3 (Hardy et al 1989a). Sixty percent of the mice exposed to 388,000 mg/m^3 died within 30 minutes (Vlachos, 1989).

Pre-narcotic signs were observed in rats (Hardy et al, 1989a) and mice (Vlachos, 1989) during inhalation exposure at levels higher than 145,500 mg/m^3.

Narcosis was induced in mice by the following exposure conditions: 388,000 mg/m^3 for 15 min; 310,400 mg/m^3 for 30 min and 198,850 mg/m^3 for 6 hours (Davies et al., 1976; Vlachos, 1989).

8.2 Repeated Exposure

No adverse clinical signs and only slight biochemical changes (no details given) were observed in rats (number and strains unspecified) exposed for 6 h/d, 5 d/w for two weeks to 48,500 mg/m^3 dichlorofluoroethane by inhalation (Pennwalt, 1987).

A four week inhalation study in rats and guinea pigs (number and strains unspecified) exposed 2h/d, 6d/w to levels of 40,000 to 50,000 mg/m^3 of dichlorofluoroethane demonstrated a reduction of bodyweight gain, minor changes in biochemical parameters (slight decrease of haemoglobin and moderate leukocitosis) and some unspecified minor changes in the liver and kidney function, and histopathological effects in the respiratory tract. In this study, the purity of the substance and specific isomer were not stated (Nikitenko and Tolgskaja, 1965).

In a 2 week inhalation study 5 groups 10m and 10f Sprague-Dawley rats were exposed 6h/d for 9 days to 0 or 24,250 to 97,000 mg/m^3 dichlorofluoroethane. Pre-narcotic signs were seen during exposure to concentrations of 41,225 mg/m^3 and higher. These signs were accompanied at 97,000 mg/m^3 by a decreased body weight gain in males and a slightly reduced food intake in both sexes. The following plasma constituents were increased at the levels indicated: glucose and AST (97,000 mg/m^3), proteins, cholesterol and sodium (70,328 mg/m^3), phosphate (41,225 mg/m^3) and calcium (24,250 mg/m^3) (Coombs et al, 1988).

In a 13 week inhalation study in which some animals were killed after 4 weeks, (4 groups each of 15m and 15f Fischer 344 rats) were exposed 6h/d, 5d/w to 9,700, 38,800 or 97,000 mg/m^3 dichlorofluoroethane. Alertness was reduced at 97,000 mg/m^3 (Yano et al, 1989, Landry et al 1989). The bodyweight and food consumption were slightly reduced in all exposed groups. However the temperature in the exposure chambers was unintentionally raised during the first period of the study and it is assumed that reduced bodyweight and food consumptions were caused by this, except perhaps for the higher concentration level. After both 4 and 13 weeks of exposure plasma cholesterol, triglyceride, and glucose

were slightly raised in the rats exposed to 97,000 mg/m^3. There were no changes in haematological or histopathological findings which could be attributed to exposure to dichlorofluoroethane.

Based on these data the no effect level of dichlorofluoroethane is 38,400 mg/m^3.

8.3 Long-term Exposure

A combined chronic inhalation toxicity/carcinogenicity study in rats with exposure levels of 7,275 to 97,000 mg/m^3, is in progress within an industry sponsored Programme for Alternative Fluorocarbon Toxicity Testing (PAFT, 1989).

8.4 Skin and Eye Irritation, Sensitisation

8.4.1 Skin irritation

Two studies were conducted on groups of 6 New-Zealand albino rabbits (Brock, 1988b; Ligett, 1988a). Application of 0.5 ml of the undiluted material to the intact skin under occlusive patch during 4 or 24 hours did not induce signs of dermal irritation during the 3 day observation period.

8.4.2 Eye irritation

Two studies were conducted on groups of 6 New-Zealand albino rabbits (Brock, 1988c; Ligett, 1988b). The undiluted material (0.1 ml) was instilled into the eyes. No signs of irritation occurred within the 3 days in one study but Brock (1988c) described dichlorofluoroethane as a mild irritant to the eye. The majority of his rabbits showed conjunctival redness, mild chemosis and blood-tinged discharge.

8.4.3 Skin sensitisation

The Magnusson-Kligman maximisation test was conducted on Hardley Dunkin guinea-pigs using the protocol specified in OECD Guideline 406 (Kynoch and Parcell, 1989). No delayed contact hypersensitivity was found in any of the 20 guinea pigs exposed to dichlorofluoroethane.

8.5 Special studies

8.5.1 Respiratory Function

3 groups of 3 male Wistar rats were exposed to 45,800 mg/m^3 dichlorofluoroethane for 25 min. No effect on respiratory frequency was observed, although there was a small change in respiratory amplitude suggesting decrease of tidal volume. It was concluded that dichlorofluoroethane is not irritant to the respiratory tract (Janssen, 1989). Repeat exposure inhalation studies have not shown morphological change in the lung. (See chapter 8.2).

8.5.2 Cardiovascular Function

The potency of dichlorofluoroethane in inducing cardiac sensitisation to adrenaline was investigated in studies in Cynomolgus monkeys and beagle dogs (Hardy et al, 1989b). The threshold of response was between 24,250 mg/m^3 and 48,500 mg/m^3 in both monkey and dog. These results were similar to CFC-11, the reference compound tested in the study.

8.6 Reproductive Effects, Embryotoxicity and Teratology

8.6.1 Reproductive Effects

No data are available. A two generation inhalation study in rats is scheduled to start in 1990 (PAFT, 1989).

8.6.2 Embryotoxic and Teratogenic Effects

3 groups of 25 pregnant female Sprague-Dawley rats were exposed to 15,520, 38,800 or 97,000 mg/m^3 of dichlorofluoroethane for 6 h/d from days 6 to 15 of pregnancy. Some clinical signs of maternal toxicity (pre-narcotic signs, pilo-erection and reduced alertness) were observed at all concentrations. At the highest concentration, salivation, hunched posture and diaphragmatic breathing, a marked increase in water consumption, a transient reduction in food intake and a marginal reduction of bodyweight gain were observed. In the 97,000 mg/m^3 exposed group, the incidence of early and late embryonic death was significantly increased. Reduced litter and mean foetal weights and retarded ossification were observed. No teratogenic effect occurred in any group (Hughes et al, 1988).

16 pregnant female New-Zealand rabbits were exposed to 6,790, 20,370 or 61,110 mg/m^3 of dichlorofluoroethane for 6 h/d from day 7 to day 19 of pregnancy. Signs of maternal toxicity including pre-narcotic signs, palpebral ptosis, respiratory disturbances and body-weight loss were observed in the 20,370 and 61,110 mg/m^3 exposed groups. There was no indication of any treatment related effects on embryo or foetal development or any evidence of teratogenicity at any exposure level (Hughes et al, 1989).

8.7 Mutagenicity

The mutagenic properties of dichlorofluoroethane were investigated in bacterial assays, chromosomal aberration assays on mammalian cell cultures in vitro and in vivo micronucleus assays.

These studies and the findings are summarised in Table 2.

When pure dichlorofluoroethane (purity > 99.5%) was tested in the Ames assay, with a vapour phase exposure, a negative response in both Salmonella typhimurium and Escherichia coli was obtained (May, 1989). Earlier studies using less pure dichlorofluoroethane gave a negative response in one study (Koorn, 1988) and a weak positive responses in two other studies with Salmonella TA 1535 in the absence of metabolic activation using a high vapour concentration exposure (Dupont, 1978; Hodson-Walker and May, 1988a). Conversely, the DNA-repair test conducted in Escherichia coli with the same material, in liquid phase, gave negative results (Hodson-Walker and May, 1988b). Furthermore, the HGPRT-assay in Chinese hamster V79 cells gave a negative response with dichlorofluoroethane in the vapour phase (Bootman et al, 1988a). Overall, it is concluded from the tests for gene mutation and the DNA-repair test, that dichlorodifluoroethane in itself does not have genotoxic potential.

Four in vitro and two in vivo clastogenicity assays were conducted. A small increase in chromosome aberrations was observed in vitro in Chinese hamster ovary (CHO) cells exposed to dichlorofluoroethane in the vapour phase (Bootman and Hodson-Walker, 1988; Hodson-Walker, 1990a). The effect was present only at high concentrations and was not influenced by the presence of S9-metabolic activation. Conversely, when the same type of cells were exposed to liquid dichlorofluoroethane no clastogenic effect was found (Wilmer and Vogel, 1988). In addition, a human lymphocyte cytogenetic assay also gave negative responses to dichlorofluroethane in vapour the phase (Hodson-Walker, 1990b).

Two micronucleus tests were performed in male and female mice. Both gave negative results after a 6 hour nose-only inhalation at concentrations ranging from 9,700 to 97,000 mg/m^3 (Bootman et al, 1988b) or a 6 hour whole-body exposure at concentrations ranging from 17,460 to 164,900 mg/m^3 (Vlachos, 1989).

The tests performed for clastogenicity suggest dichlorofluoroethane may have weak in vitro clastogenic activity on CHO cells. The inconsistency between the findings in tests using vapour and liquid exposures and

hamster cells and human cells make the interpretation difficult. The lack of effect of dichlorofluoroethane in the micronucleus assay in mice suggests that the weak *in vitro* clastogenic action apparent in CHO cells, if real, would not be expressed *in vivo*.

Based on the overall weight of evidence it is concluded that dichlorofluoroethane does not demonstrate toxicologically significant mutagenic activity.

8.8 Carcinogenicity

No data are available. A combined chronic inhalation toxicity/carcinogenicity study in rats with exposure levels of 7,275 to 97,000 mg/m^3 is in progress under the sponsorship of PAFT (1989).

9. EFFECTS ON MAN

There are no reported adverse health effects which can be ascribed to dichlorofluoroethane.

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Table 1. Physical and Chemical Properties of Chlorodifluoroethane

Molecular weight	:	117	
Physical form	:	liquid	
Colour	:	colourless	7)
Boiling point, °C at 1013 HPa	:	32	1)
Freezing point, °C	:	- 103,5	7)
Liquid density at 20°C, g/cm3	:	1.24	2)
Vapour density at boiling point, kg/m3	:	4.82	7)
Solubility in water, g/l at 25°C	:	4 - 13	4)
Solubility in long chain polyols, % (by weight)	:	24.4	7)
Fat solubility	:	soluble	7)
Vapour pressure at 25°C, KPa	:	76.3	3)
Flammability	:	non flammable	6)
Octanol/water partition coefficent	:	2.3	5)

Ref Research and Consulting Company b.v. The Netherlands (1989) RCC NOTOX Proj. No. :

1) 006143
2) 006154
3) 006165
4) 006187
5) 006198
6) 006211
7) ATOCHEM (1989) Internal Data.

Table 2. The Genetic Toxicology of Dichlorofluoroethane in in vitro and in vivo Studies

ASSAY	STRAIN/TYPE	METABOLIC ACTIVATION	RESULTS	COMMENTS	SAMPLE PURITY (%)	REFERENCES
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537 TA 1538	+/- S-9	TA 1535 weakly positive with & without S-9	Vapour phase tested	<99.5	Dupont, 1978
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA1537 TA 1538	+/- S-9	TA 1535 positive with & without S-9 at 10-20% conc.	Vapour phase tested up to 30%	99.6	Hodson-Walker and May, 1988a
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537 TA 1538	+/- S-9	negative	Vapour phase tested up to 30%	99.95	May, 1989*
Salmonella typhimurium (Ames test)	TA 98, TA 100, TA 1535, TA 1537 TA 1538	+/- S-9	negative	Vapour phase tested up to 42%	97.6	Koorn, 1988
Escherichia coli (Ames test)	WP2 uvr A tryptophan dependent	+/- S-9	negative	Vapour phase tested up to 30%	99.95	May, 1989*
HGPRT Test Chinese Hamster cells	V 79 cell	+/- S-9	negative	Vapour phase tested up to 35%	99.6	Bootman et al, 1988a

Table 2. The Genetic Toxicology of Dichlorofluoroethane in in vitro and in vivo Studies (cont.)

ASSAY	STRAIN/TYPE	METABOLIC ACTIVATION	RESULTS	COMMENTS	SAMPLE PURITY (%)	REFERENCES
Escherichia coli DNA Repair	WP2, WP67, CMB71	+/- S-9	negative	Liquid phase tested up to 10 mg/ml	99.6	Hodson-Walker and May, 1988b
Chromosomal aberration	C.H.O.	+/- S-9	negative	Vapour phase tested up to 13.2 mg/ml	99.5	Wilmer and Vogel, 1988
Chromosomal aberration	C.H.O.	+/- S-9	positive with & without S-9	Liquid phase tested up to 35%	99.6	Bootman and Hodson-Walker 1988
Chromosomal aberration	C.H.O.	+/- S-9	positive with & without S-9	Vapour phase tested up to 10%	99.83	Hodson-Walker, 1990a*
Lymphocyte cytogenetic	Human lymphocytes	+/- S-9	negative	Vapour phase tested up to 35% (1988)	99.83	Hodson-Walker, 1990b*
Bone-marrow Micronucleus	Mice (CDI)	in vivo testing	negative	2,000 - 8,000 20,000 ppm/6h	99.6	Bootman et al, 1988b
Bone-marrow Micronucleus	Mice (CDI)	in vivo testing	negative	3,600 - 10,000 34,000 ppm/6h	99.98	Vlachos, 1989*

* PAFT II. data

APPENDIX 1

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The Task Force wishes to thank Dr C. DE ROOIJ, Solvay, Brussels, for his valuable contributions to this report.

APPENDIX 2

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