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Document Processing Center (TS-790)
Attention: (8e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

MR 40074

Ladies and Gentlemen:

Subject: Notice in Accordance with TSCA Section 8(e) – Results of a Subacute Inhalation Toxicity Study with BAS 090 00 S (CAS No.: 68002-96-0, Fatty Alcohol Ethoxylate Propoxylate) conducted by BASF Aktiengesellschaft, Ludwigshafen, Germany – Refer to EPA Document Control Number 8EHQ-0897-14002

In an earlier submission dated August 19, 1997, we reported data on an acute inhalation toxicity study with the test substance. Subsequently, a subacute inhalation study was performed as follows:

Five male and five female Wistar rats per test group were head-nose exposed to dynamic atmospheres of BAS 090 00 S liquid aerosols for 6 hours per working day for about 28 days (20 exposures). The target concentrations were 0.5, 1.0, 2.5 and 25 mg/m³. A concurrent control group was exposed to an aqueous ethanol solution as used for dilution of the test substance.

The target concentrations were fully met in a stable fashion. The particle size distributions yielded mass median aerodynamic diameters between 1.2 and 1.7µm.

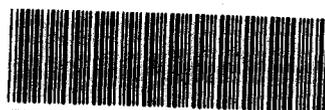
The inhalation of 25 mg/m³ BAS 090 00 S aerosols by male and female rats for a period of 4 weeks caused toxicity to the respiratory tract characterized by inflammatory and/or epithelial changes in nasal cavity, larynx, trachea and lung. The severity of the lung changes led to general effects induced by hypoxia and/or stress (e.g., premature death of animals, respiratory dysfunction, reduced general health, polycythemia, increased polymorphonuclear counts and other unspecific clinicopathological or histopathological findings). In spite of these marked health effects, no neurofunctional impairment was obvious in the surviving animals of the high concentration group during and at the end of the exposure period.

The No Observed Adverse Effect Concentration (NOAEC) for genuine systemic toxicity is 25 mg/m³, based on the interpretation that the effects on general health observed in the study are secondary to severe lung injury. The NOAEC for lower respiratory tract (lung) is 2.5 mg/m³ and the NOAEC for upper respiratory tract (larynx) is 1 mg/m³.

The results described above are in line with those of some other polyalkylene glycols (ECETOC 1997) producing similar respiratory tract effects. Therefore these findings are not considered to be unexpected because of the chemical nature of the test article. Additionally, the study has been conducted according to guideline requirements using particles with aerodynamic diameters of 10 µm and less. In agricultural practice, however, particles with aerodynamic diameters of 30 µm and more are formed during spraying.

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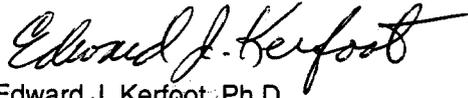
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Therefore the hazard potential described by the subacute inhalation toxicity study is not representative of handling and use of the test substance in agricultural preparations. Respirable aerosols are not generated under these circumstances and a subacute inhalation exposure of the user cannot occur. Nonetheless, BASF Corporation understands that the reporting of the study results is in accordance with EPA's policy.

If you have any questions, please call me at 734-324-6207.

Very truly yours,

BASF CORPORATION



Edward J. Kerfoot, Ph.D.

Director, Toxicology and Product Regulations

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TITLE

Rationale for Non-Classification of BAS 090 00 S concerning
Repeated Exposure Inhalation Toxicity

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This document contains 9 pages

Rationale for Non-Classification of BAS 090 00 S concerning Repeated Exposure Inhalation Toxicity

1. BACKGROUND

National and international toxicity testing guidelines for inhalation studies require to test liquid aerosols and dusts applying particle sizes respirable in the test species used, in order to elucidate the toxic potential of a material if deposited throughout the entire respiratory tract. For the common test species rat, the mean aerodynamic particle sizes required are $\leq 4 \mu\text{m}$. To reach this small particle size, powders usually have to be micronized and liquid aerosols have to be generated using technical equipment for particle size selection.

It is present practice in the European Union to require classification and labeling of the tested materials concerning their acute inhalation hazard based on the results of inhalation toxicity studies without considering if respirable aerosols may be produced under conditions of normal handling and use. Technical modifications of a material to reduce the proportion of respirable fractions during application usually do not modify classification and labeling.

The EU chemicals regulation concedes, however, that classification and labeling should be mainly based on toxicity tests reflecting conditions occurring under normal handling and use. As this is not yet implemented for inhalation toxicity data, an ad hoc working group at the VCI elaborated a rational approach in the use of inhalation toxicity studies for classification and labeling taking into account possible exposure caused by normal handling and use of a compound. It is described in the Technical Guidance Document: "Acute Inhalation Toxicity Testing" (Draft of May 28, 1999).

Basically it is suggested, that powders of solid substances and liquid aerosols in technical applications should be considered as preparations containing a certain amount of particles of toxicological relevance. Particles of toxicological relevance are defined as those capable to enter the thoracic region of the respiratory tract in humans. The mass fraction of particles of toxicological relevance may be calculated from the particle size distribution measured in powder materials or defined spraying applications and the deposition probability curve of particles of toxicological relevance as defined above. Using the EU preparations directive or modifications thereof, the calculated mass fraction then determines the classification of the inhalation hazard of materials.

This approach was used in this rationale to show that labeling of agricultural formulations containing BAS 090 00 S on the basis of inhalation study results with this compound is not indicated.

2. INHALATION TOXICITY DATABASE

BAS 090 00 S was tested in an acute and a subacute inhalation toxicity study. The following results were obtained:

Acute inhalation toxicity study:

For determination of the acute inhalation toxicity (single 4-hour-exposure) of BAS 090 00 S as a liquid aerosol, a study in male and female Wistar rats was performed according to OECD-Guideline method 403. The following concentrations were tested: 0.094, 0.26, 0.59 and 5.5 mg/l. Cascade impactor measurements revealed particle size distributions with mass median aerodynamic diameters which were in the respirable range. No mortality occurred at the low and intermediate concentrations. All females and 4/5 males as well as all animals died at 0.59 or 5.5 mg/l, respectively. The LC50 for male and female animals was estimated to be $0.26 < LC50 < 0.59$ mg/l.

Subacute inhalation toxicity study (OECD method 412):

Five male and five female Wistar rats per test group were head-nose exposed to dynamic atmospheres of BAS 090 00 S liquid aerosols for 6 hours per working day for about 28 days (20 exposures). The target concentrations were 0.5, 1.0, 2.5 and 25 mg/m³. A concurrent control group was exposed to an aqueous ethanol solution as used for dilution of the test substance.

The target concentrations were fully met in a stable fashion. The particle size distributions yielded MMADs between 1.2 and 1.7 µm.

The inhalation of 25 mg/m³ BAS 090 00 S aerosols by male and female rats for a period of 4 weeks caused toxicity to the respiratory tract characterized by inflammatory and/or epithelial changes in nasal cavity, larynx, trachea and lung. The severity of the lung changes led to general effects induced by hypoxia and/or stress (e.g. premature death of animals, respiratory dysfunction, reduced general health, polycythemia, increased polymorphonuclear counts and other unspecific clinico-pathological or histopathological findings). In spite of these marked health effects, no neurofunctional impairment was obvious in the surviving animals of the high concentration group during and at the end of the exposure period.

The No Observed Adverse Effect Concentration (NOAEC) for genuine systemic toxicity is 25 mg/m³, based on the interpretation that the effects on general health observed in the study are secondary to severe lung injury. The NOAEC for lower respiratory tract (lung) is 2.5 mg/m³ and the NOAEC for upper respiratory tract (larynx) is 1 mg/m³.

3. DISCUSSION OF INHALATION TOXICITY RESULTS

Exposure of rats to respirable aerosols of BAS 090 00 S caused local toxic effects in the respiratory tract. Systemic signs of toxicity encountered in the inhalation studies including mortality, are interpreted to be secondary to concentration dependent severity of lung lesions induced by the respirable parts of the aerosol.

The respirability of the tested aerosols is documented in the particle size distributions measured during the course of the studies. The following table shows that these aerosols

contained high fractions of respirable particles with the potential to deposit in the alveolar region of the lung.

Study	Conc. Range [mg/m ³]	Mean MMAD [µm]	Mean GSD	Respirability [%]
Acute	94 - 5500	< 1.2 (0.4)	3.9	94,5
Subacute	0.5 - 25	1.45	2.1	84

The differences in particle size distributions between acute and subacute study can be explained in the different generation techniques used for the different concentration ranges in either of the studies. Furthermore the resolution range of the impactor used for high concentrations is limited, leading to increased extrapolation uncertainties if the particle size distribution is approaching the lower border of the measuring range (1.2 µm).

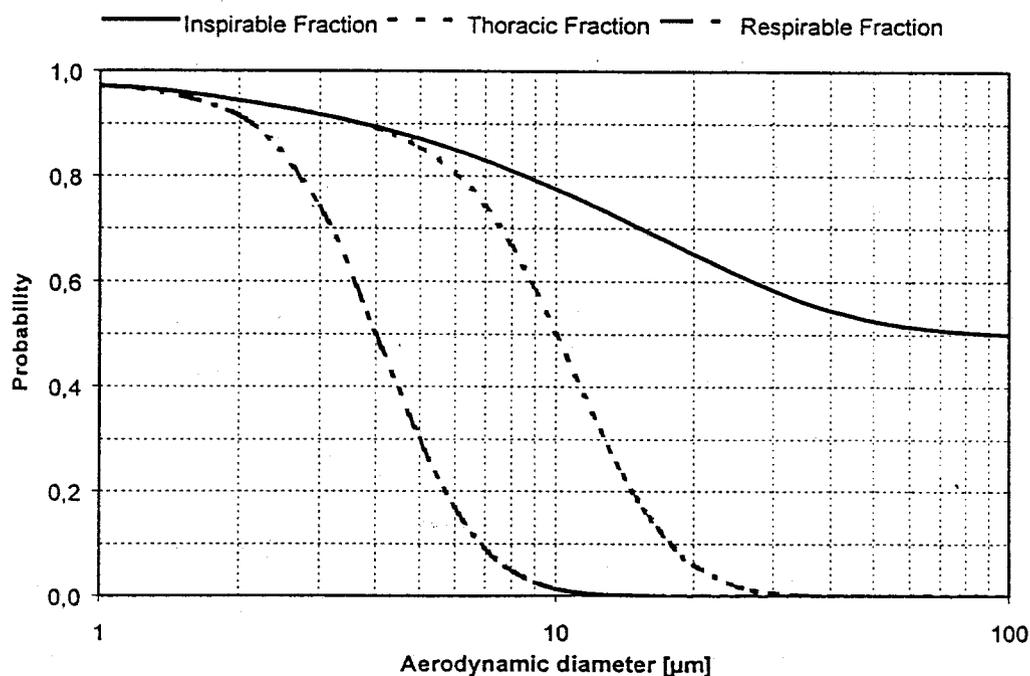
4. IMPORTANCE OF PARTICLE SIZE DISTRIBUTION FOR TOXIC EFFECTS

The particle size distributions of aerosols and dusts determine the deposition of inhaled particles within the various regions of the respiratory tract. Usually three size fractions are used to describe the behaviour of particles:

1. Inspirable fraction: Particles which are able to enter the nose
2. Thoracic (inhalable) fraction: Particles which are able to pass the larynx and reach the tracheo-bronchial and alveolar region
3. Alveolar (respirable) fraction: Particles which are able to reach the alveolar region

Figure 1 displays the deposition probabilities of the three size fractions in humans in the (respective region of the) respiratory tract (DIN EN 481, Sep. 93).

Figure 1: Particle deposition probabilities in humans



It is obvious from these curves, that the probability for aerosol particules to reach the deep lung in humans is negligible at aerodynamic diameters of 10 μm or above and particles with diameters above 30 μm will not be deposited in the tracheo-bronchial region at all. Therefore only aerosols which contain thoracic or alveolar particle size fractions can cause toxic effects in the deep respiratory tract.

5. COMPARISON OF TEST AND FIELD CONDITION AEROSOLS

BAS 090 00 S is used in agricultural formulations up to 25%. These formulations are diluted in a ratio from 1:100 to 1:600, depending on crop to be treated and application technique. For example for fungicide applications in cereals an amount of water of 200 – 400 l/ha is used. Most of the formulated products have an application rate of 1 l/ha.

The spray liquids as used in agricultural applications are typically applied with flat jet nozzles. A typical nozzle would be an extended range flat jet nozzle with an application angle of 110 degrees (for example: XR 110 02 ; throughput rate 0.2 gal/min), used at a pressure range of 1 to 3 bar.

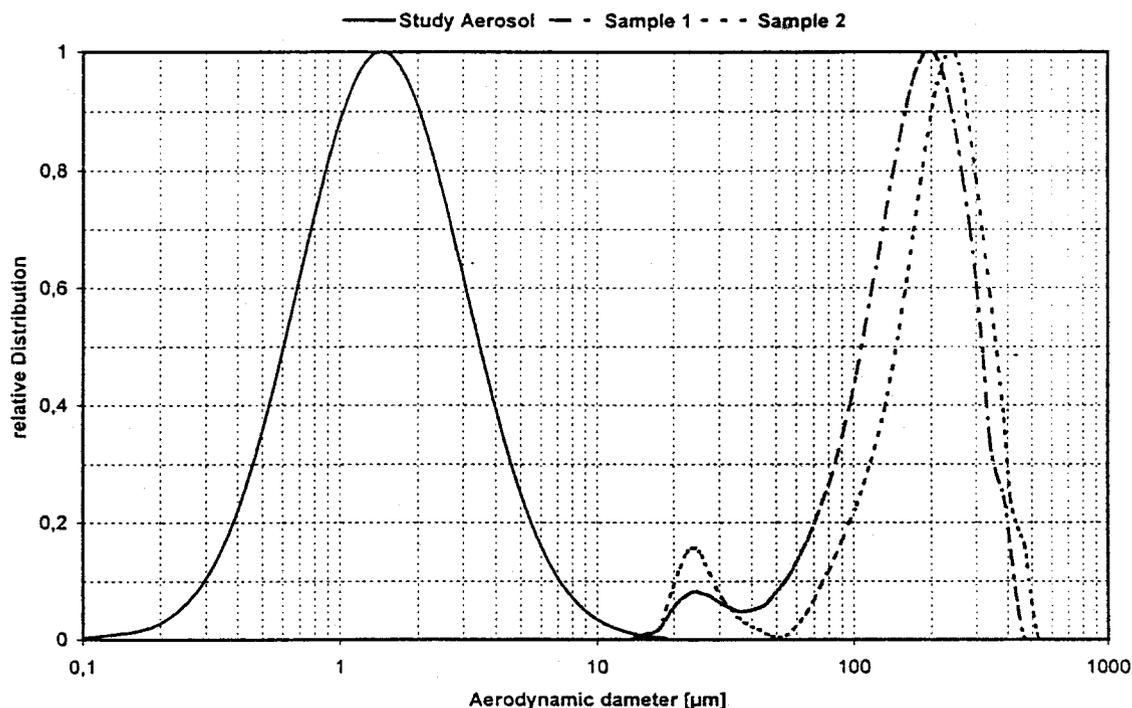
Particle size measurements of agricultural aerosols reveal volume distributions with mean droplet diameters of 150 - 500 μm . Nozzles with small mass flow rates produce small droplets, nozzles with larger mass flow rates produce larger droplets. The higher the pressure is, the smaller the droplet size will be. The mean volume droplet diameter is equal to the mass median diameter because the density of agricultural formulations in application concentration is approximately 1 kg/l. The GSD is in a range of 1.3 to 1.9.

To obtain specific information about the particle size distribution of application aerosols containing BAS 090 00 S, two tests were performed: The formulation of Sample 1 contains 6.7 % BAS 090 00 S. It is used in a concentration of 1 l/ha in an amount of 300 l/ha water. The formulation of Sample 2 contains 25 % BAS 090 00 S and is used under the same conditions. For Sample 1 the concentration of BAS 090 00 S is 0.223 g/l, for Sample 2 it is 0.833 g/l. For representative use in field crops the spraying applications were run with flat jet nozzles XR 110 02 at pressures of 3 bar.

Laser scattering in a Malvern MASTER SIZER SX was used to analyze the particle size distributions of generated aerosols. The principle is based of laser ensemble light scattering. This systems can be used for measurements of sprays, aerosols, dispersible powders or multiphase fluids. (ISO/FDIS 13320-1, 1999 "Particle size analysis – Laser diffraction methods")

The Master Sizer SX has an optical range of 0.5 μm to 600 μm with a 300 mm lens. The temperature during the measuring period was between 20 – 26° C; the relative air humidity was between 70 – 80%. The measurement took place in a system, in which the nozzle was positioned in a vertical distance of 0.4 m to the laser beam. During spraying of the Samples 1 and 2 at least 2000 to 5000 droplets were measured. Figure 2 shows the normalized distribution curves for the volumetric distribution of the droplets generated by spraying. It is evident, that the particle fractions being able to enter the deep lung (< 10 μm) are negligible. In figure 2 the particle size distribution of the aerosol produced in the inhalation toxicity studies is compared to the application aerosols. As might be easily seen, the application aerosols do not contain any considerable quantity of particles in the range used for the toxicity studies.

Figure 2: Particle size distribution in inhalation study and application aerosols



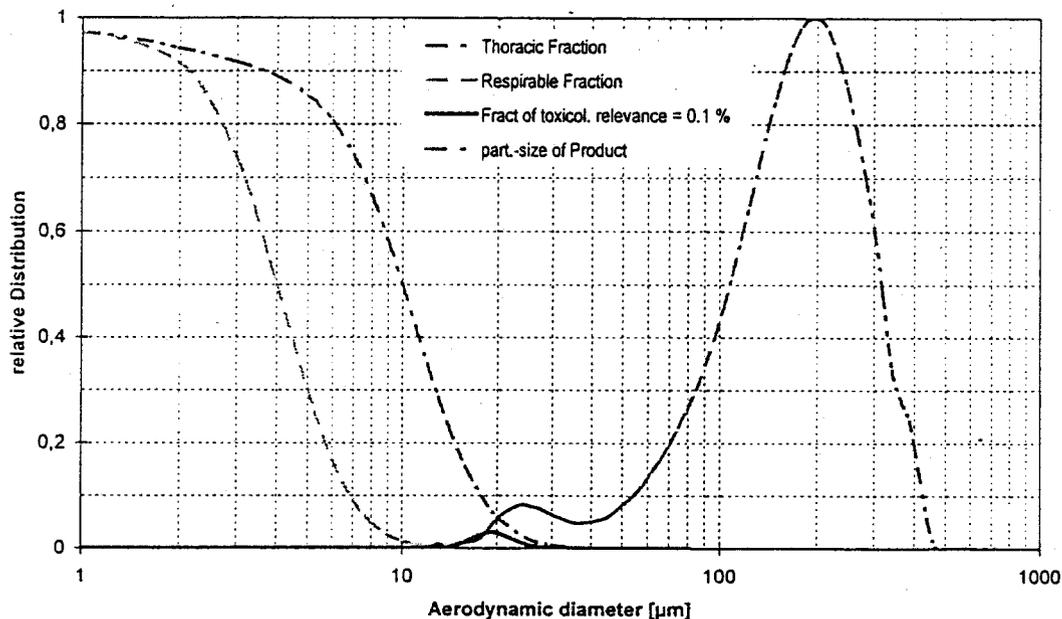
6. COMPARISON OF AEROSOLS TESTED IN INHALATION STUDIES AND PRESENT UNDER NORMAL HANDLING AND USE

Furthermore, in using the deposition probability curve for thoracic particles, as shown in Figure 1, the fraction of aerosol considered to be of toxicological relevance for inhalation in humans can be calculated.

In figures 3 and 4 the integral under the particle size distribution curve of the application aerosol is considered 100%. The deposition probability curve for the respirable and the thoracic fraction are plotted as well. The multiplication of the thoracic fraction deposition probability and the measured particle size distribution under application conditions at a given particle size defines the fraction of particles of toxicological relevance as described above. The area under the curve of the fraction of particles of toxicological relevance determines the hazard of the application aerosol.

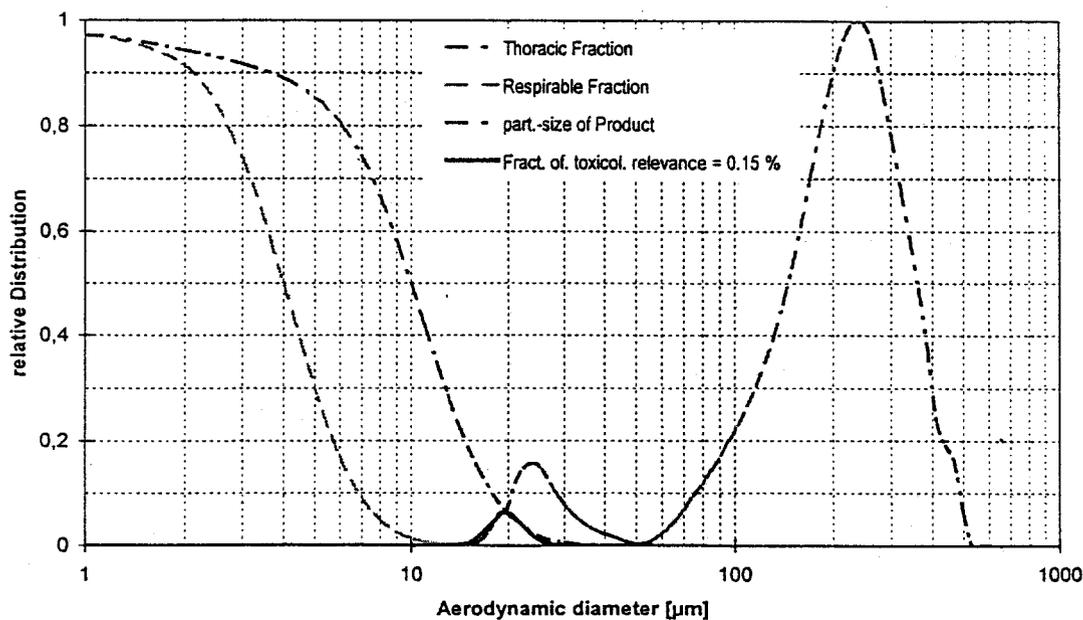
In sample 1 (figure 3) the median particle diameter MMAD is 167,5 μm. The amount of droplets smaller than 10 μm is 0%, smaller than 30 μm are 3.3% of the droplets. An amount of 0.1 % of the particles is in the size range of toxicological relevance. Thus in sample 1, containing 67 g/l of BAS 090 00 S in the formulation and, therefore, are applied per ha, only an amount of 67 mg /ha occurs in a droplet size of toxicological relevance.

Figure 3: Formulation with 6.7% of BAS 090 00 S (Sample 1— part.-size of product)



In sample 2 (figure 4) the median particle diameter MMAD is 204 μm. The amount of droplets smaller than 10 μm is 0%, smaller than 30 μm are 6% of the droplets. The higher percentages of particles below 30 μm, as compared to the results with sample 1, are due to a second peak in the distribution at small particle sizes. An amount of 0.15 % of the particles is in the size range of toxicological relevance. Thus in Sample 2, containing 250 g/l of BAS 090 00 S in the formulation and, therefore, applied per ha, only an amount of 375 mg/ha occurs in a droplet size of toxicological relevance.

Figure 4: Formulation with 25 % of BAS 090 00 S (Sample 2 – part.-size of product)



Conclusion:

In application aerosols of BAS 090 00 S containing formulations used in the common dilution for field crops and produced by standard extended range nozzles under standard pressure and weather conditions less than 0.2 % of the aerosol consists of particles with dimensions of toxicological relevance. That means, that under the estimated use conditions, less than 0.2 % of the material quantities used, are of toxicological relevance as determined by the above inhalation studies.

7. REGULATORY CONSEQUENCES

The only intended use of BAS 090 00 S is that of a formulant in plant protection products.

It was demonstrated in the foregoing chapters, that inhalation toxicity test guidelines require experiments to be carried out by generating small respirable particles. The possible intrinsic hazard identified by such toxicology studies is depending on physical conditions as generated in the study and might be artificial. At the work place or under field condition, e.g. during mixing, loading and especially application of plant protection products, the fraction of particles of toxicological relevance is very limited only. Therefore, under conditions of normal handling and use, the effect as indicated in the inhalation studies is not possible to occur.

If the use of a compound is clearly restricted to applications where particles of toxicological relevance are not generated, classification gives no reason. This is in line with the EU - Directives for classification and labeling. It is e.g. stated in the EU - Directive 93/21/EEC (18. Amendment to 67/548/EEC) under para 3.1.1: " If adequate evidence is available to demonstrate in practice that the toxic effect of substances and preparations on man is, or is likely to be different from that suggested by the experimental results obtained in animal tests or by the application of the conventional method referred to in Article 3 (5) of Directive 88/379/EEC then such substances and preparations should be classified according to their toxicity in man." This is underlined in para 3.1.4 of the same Directive as follows: "When the classification is to be established from experimental results obtained in animal tests the result should have validity for man in that the tests reflect, in an appropriate way, the risks to man.

The conclusions derived from this para is stated in the introduction of the Directive 91/414/EEC for the Annex II requirements for the dossier to be submitted for the inclusion of an active substance in Annex I. "The information shall include: a technical dossier supplying the information necessary for evaluation the foreseeable risks, whether immediate or delayed, which the substance may entail for humans". However, certain pieces of information which would not be necessary owing to the nature of the substance or of its proposed uses need not be supplied. In such cases, or where it is not scientifically necessary or technically possible to supply information, a justification which is acceptable to the Commission in accordance with Article 6 must be submitted.

For labeling reference is made to para 1.4 which reads:

"The label takes account of all potential hazards which are likely to be faced in the normal handling and use of dangerous substances and preparations when in the form in which they are placed on the market....".

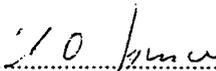
Since the potential or intrinsic hazard of the study is not present during normal handling and use, labeling of the compound or the preparations is obsolete. Hazard labeling is also not rectified for the compound since in all situations until final application conditions for this possible hazard do not exist. Further to this considerations, referring back to a suggestion cited in the "background" chapter (1), BAS 090 00 S containing agricultural aerosols could be considered like preparations containing <0.2% of a toxic component.

8. FINAL CONCLUSION FOR CLASSIFICATION

The considerations and discussions in the preceding chapters demonstrate, that no hazard to man as may be indicated by the result of the guideline inhalation toxicity study is given under the intended agricultural use of BAS 090 00 S and formulations containing it. Therefore there is no reason for classifying BAS 090 00 S containing formulations on the basis of the 28-day study.



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