

B. Toxicological Profile

1. *Acute toxicity.* Based on available acute toxicity data, dimethenamid and dimethenamid-P do not pose an acute dietary risk. The acute toxicity studies place both technical materials in acute toxicity category II for acute oral; in acute toxicity category III for acute dermal, inhalation, and eye; and in acute toxicity category IV for dermal irritation. The technical materials are a positive skin sensitizer.

2. *Genotoxicity.* The following testing was performed with dimethenamid for genotoxicity. A modified ames test: Negative; *in vitro* CHO/HGPRT mammalian cell mutation assay: Negative; *in vitro* cytogenetics - CHO cells (1 study; chromosome aberrations): Weakly positive; *in vitro* UDS test using rat hepatocytes (3 studies; DNA damage and repair): 2 negative; 1 equivocally positive, mouse micronucleus assay (2 studies; chromosome aberrations): Negative, rat dominant lethal assay: 1 study equivocally positive, 1 study negative. Overall dimethenamid has been tested in 14 genetic toxicology assays. The weight of the evidence demonstrates that dimethenamid is not genotoxic.

The following testing was performed with dimethenamid-P for genotoxicity. A modified ames test (3 studies; point mutation): Negative; *in vitro* CHO/HGPRT mammalian cell mutation assay (1 study; point mutation): Negative; *in vitro* cytogenetics - CHO cells (1 study; chromosome aberrations): Negative; *in vitro* UDS test using rat hepatocytes (1 study; DNA damage and repair): Negative; mouse micronucleus assay (1 study; chromosome aberrations): Negative. Dimethenamid-P has been tested in a total of 7 genetic toxicology assays. These assays were performed both *in vitro* and *in vivo* and multiple assays were conducted for each of the three EPA Guideline requirement categories. Based on the data presented above, the data indicates that dimethenamid-P does not induce gene mutations, is not clastogenic and does not induce other effects indicative of genotoxicity. Therefore, BASF concludes that dimethenamid-P does not pose a mutagenic hazard to humans.

3. *Reproductive and developmental toxicity—i. Rat.* A developmental rat study using dimethenamid via oral gavage resulted in dosages of 0, 50, 215, and 425 milligram per kilogram (mg/kg)/day with a development toxicity no observed adverse effect level (NOAEL) of 215 mg/kg/day and a maternal toxicity of 50 mg/kg/day based on the following: (1) Signs of maternal toxicity, in the form of reduced body weight gain

and food consumption, increased liver weight and clinical observations were observed at dose levels > 215 mg/kg/day with an increase in effects to the upper dose level; (2) at the = 215 mg/kg/day dose levels slight decreases in fetal body weights were observed which are not indicative a teratogenic effect; and (3) at the 425 mg/kg/day dose level a slight increase in resorptions was observed, and two fetuses had incomplete ossified manubria. These effects are not indicative of a teratogenic effect.

A developmental rat study using dimethenamid-P via oral gavage resulted in dosages of 0, 25, 150, and 300 mg/kg/day with a development toxicity NOAEL of 25 mg/kg/day and a maternal toxicity of 25 mg/kg/day based on based on the following: (1) Signs of maternal toxicity, in the form of decreased body weights and food consumption were observed at dose levels > 150 mg/kg/day with an increase in effects to the upper dose level; (2) at the 150 mg/kg/day dose level slight decreases in fetal body weights and retarded ossification of the pelvis pubis were observed which are not indicative a teratogenic effect; and (3) at the 300 mg/kg/day dose level slight decreases in fetal body weights, microphthalmia in two fetuses/two litters, distended ureters, and retarded ossification of the 2nd sternal centra and pelvis pubis were observed, similarly, these effects are not indicative of a teratogenic effect.

ii. *Rabbits.* A developmental study in rabbits using dimethenamid via oral gavage resulted in dosages of 0, 37.5, 75, and 150 mg/kg/day (HDT) with a development toxicity NOAEL of 75 mg/kg/day and a maternal toxicity of 37.5 mg/kg/day based on: (1) Decreased body weight, food consumption, and absorption/premature delivery in the 75 and 150 mg/kg/day dose groups; and (2) effects on fetal development were a low incidence of absorption/premature delivery and hyoid angulated changes in the 150 mg/kg/day dose group which are not are indicative of a teratogenic effect.

iii. *Two-generation reproduction - rats.* A two-generation reproduction study using dimethenamid with rats fed dosages of 0, 7.5, 38, and 155 mg/kg/day (average mg/kg/day dose levels for both male and female rats) with a reproductive NOAEL of 38 mg/kg/day and with a parental NOAEL of 38 mg/kg/day based on: (1) Parental toxicity as evident by reduction in body weight and food consumption and significant increases in absolute and/or relative liver weights in both males and female rats in the 155 mg/kg/day dose group; and (2) significant reductions in pup weight during lactation were observed

in the 150 mg/kg/day dose group. No changes in pregnancy rates, fertility or length of gestation were observed at all dose levels tested.

4. *Chronic feeding and carcinogenicity.* The established reference dose (RfD) for dimethenamid and dimethenamid-P is based on a 2-year feeding study in rats with dimethenamid, with a threshold NOAEL of 5.1 mg/kg/day. Using an uncertainty factor of 100, the RfD is calculated to be 0.05 mg/kg/day. The following are summaries of the pertinent toxicity data supporting dimethenamid tolerances:

i. *Chronic feeding - nonrodent.* A 1-year feeding study in dogs fed dimethenamid at dosages of 0, 2, 9.6, or 49 mg/kg/day with a NOAEL of 9.6 mg/kg/day based on the following effects: (1) Slight decreases in body weights for both the high dose male and female dogs as compared to controls; (2) a variable degree of periportal hepatocyte vacuolation in the high-dose male and female dogs; (3) minimal or mild hepatocyte enlargement was similarly observed in the high-dose dogs; and (4) the liver changes at the high-dose group correlated with increase in serum alkaline phosphatase activity and cholesterol levels and increased liver-to-body weight ratios in both male and female dogs.

ii. *Chronic feeding/carcinogenicity - rat.* A combined chronic feeding/carcinogenicity study using dimethenamid was performed in rats being fed dosages of 0, 5.1, 36, and 80 mg/kg/day (males) and 0, 6.8, 49, and 109 mg/kg/day (females) with a NOAEL of 5.1 mg/kg/day (males) and 6.8 mg/kg/day (females) based on the following effects: (1) Decreased body weights in both males and female rat at dose levels > 36 mg/kg/day dose groups with a slight progression of severity to the upper level; (2) decreased food consumption in both males and female rats at dose levels > 36 mg/kg/day dose groups with a slight progression of severity to the upper dose level; (3) minimal hematological and clinical chemistry value changes at dose levels > 36 mg/kg/day dose groups with very slight increase of severity at the higher dose tested; (4) increased absolute liver weights for females at dose levels > 49 mg/kg/day; (5) microscopic findings were observed in the liver, parathyroid, and stomach of high-dose males, only, and ovaries of high-dose females; and (6) an increased incidence of benign and malignant tumors of the liver at the highest dose level tested. The liver tumors observed in this study occurred at an incidence which was slightly beyond the historical control range for this tumor type, and occurred at the